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Aspects for Thiocarbamoylation: Synthesis and Pharmacological Screening of Novel Thiophene, Thiadiazole and Pyrazole Derivatives

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ABSTRACT

Background: The aim of the present work is to synthesize a new series of thiophenes, thiadiazoles and pyrazoles by convenient and facile method with hope to discover more potent drugs as antidepressants and antifungi. **Materials and Methods:** The synthesized compounds were synthesized by two alternative methods. The targeting compounds were tested as antidepressant and antifungi by using male albino mice (20-24 g) in the forced swimming test under standard conditions with free access to food and water and agar-diffusion method, respectively. **Results:** The synthesized compounds could be considered as valuable templates for further modification or derivatization to design more potent antidepressant agents. The findings of this study illustrate that thiadiazole cycles of 13a-c exhibit more potency as antidepressants and antifungi than their analogous which contain thiophenes and pyrazole ring. **Conclusion:** Reactivity of the synthesized compounds vary according to the newly cyclized ring. As number of heteroatoms increase inside the ring especially sulfur atom, reactivity increases. Also, as electron withdrawing group increases, reactivity increases.

Key words: Antidepressant, thiophenes, pyrazole, thiadiazoles, thiocarbamoyl, antifungi

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INTRODUCTION

Increasing evidence suggests that thiocarbamoyl pyrazoline derivatives possess a broad spectrum of biological activities such as anti depressant (Ozdemir *et al*., 2008; Gokhan *et al*., 2003), anti ameabic (Budakoti *et al*., 2006; Abid and Azam, 2005, 2006), potential analgesics, MAO inhibitors (Ruhoglu *et al*., 2005), antimicrobial activity, herbicidal activity (Usui *et al*., 2013; Sherman *et al*, 1991), antineoplastic activity, anticonvulsant activity, antiepileptic, anti-inflammatory activity, CNS activity and chemotherapy. The discovery of this class of drugs provides an outstanding case history of modern drugs development. It also points out the unpredictability of biological activity from structural modification of a prototype drug molecule. Earlier studies by Ozdemir *et al*. (2007), Soni *et al*. (1987) demonstrated that 1,3,5- triphenyl-2-pyrazolines have Monoamine Oxidase (MAO) inhibitory activities. In this strategy, the sulfur atom is a part of a reactive thiocarbonyl, a functional group which can modulate molecular reactivity. It has been found that it has an ample use in synthesis (Motherwell and Crich, 1992; Barton and Parekh, 1992; Curran *et al*., 1995). Fungicides are an important class of chemicals used widely for the protection of crops. A systemic fungicide is defined as a systemic fungi toxic compound that controls a fungus pathogen remote from the point of application and that can be detected or identified. These compounds are absorbed by the plant and get translocated within it, thus providing protection as well as eradicating already established infection. It is known that a great variety of reactants bearing the N = C = S fragment undergoes cyclization on reaction with γ-halocarbonyl compounds to afford thiophenes (Fadda *et al*., 2000; Abdel-Latif and Bondock, 2006; Brannock *et al*., 2011; Do and Kim, 2011; Sastri, 1998), thiazoles, 2,3-dihydrothiazoles (Yang, 2008), which have been shown to exhibit antiprotozoal (Valderrama *et al*., 1999) and fungicidal properties (Alomar *et al*., 2012).

Rasha E. El-Mekawy has been particularly interested to study if reactions of such thiocarbamoyl might be extended to include a more general synthesis of other classes of organic compounds and its utility as synthetic intermediate for the synthesis of new heterocyclic compounds. The present work reports on the synthesis of several new thiophene derivatives by the reaction of thiocarbamoyl of the type with compounds containing an active methylene group in the presence of a base. Reactions of this type have not been reported previously, but were found to give products in excellent yields under very mild conditions. Moreover, the resulting thiophene derivatives have latent functional substituents which have potential for further chemical transformations and new routes for the preparation of substituted thiophene

derivatives with possible biological activity. Herein, it is good to report an excellent finding about efficient procedure for the synthesis of otherwise inaccessible heterocyclic ring system, utilizing phenyl isothiocyanate as a key starting material and examined their activities as antidepressant and antifungi agents.

MATERIALS AND METHODS

Chemistry: Melting points were taken in open capillary tubes using an electrothermal apparatus 910 (Rochford, UK) and are uncorrected. Microanalyses were performed using an Elementary Vario el III C, H, N, S. IR, ^{1}H NMR and mass spectra were recorded at the Microanalytical Center, Faculty of Science, Cairo University. Tranylcypromine sulfate was supplied by Sigma Chemical.

3-Oxo-3-(5-(trifluoromethyl)-1H-indazol-1-yl)propanenitrile (1): The solution of 2-cyano acetohydrazide (0.99 g, 0.01 moL) and 2-hydroxy-5-(trifluoromethyl) benzaldehyde (1.99 g, 0.01 moL) in absolute ethanol containing few drops of pipridine) was refluxed for 3 h. The product was poured into ice water. The crude product which was separated out was filtered and crystallised from proper solvent.

Yellow crystals; m.p. 250°C; yield 77 %; IR (KBr): ύ cm^{-1} = 3142 (=CH of olefinic group), 2251 (CN), 1645 (C=O), 1586 (C=N); ^{1}H-NMR (DMSO-d_6) δ/ppm = 3.10 (s, 2H, CH_2), 5.89 (s, 1H, CH), 6.54 (s, 1H, Ar-H), 6.94 (d, 1H, Ar-H), 6.99 (d, 1H, Ar-H). MS: (m/z, %) 253 (M^+, 26%), 227 (53%), 158 (47%), 144 (69%), 116 (89%), 77 (100%), 65 (23%). Anal. Calcd for $C_{11}H_6F_3N_3O$ (253.2): C, 52.18; H, 2.39; N, 16.60%. Found: C, 52.20; H, 2.40; N, 16.63%.

(E)-3-mercapto-3-(phenylamino)-2-(5-(trifluoromethyl)-1 H-indazole-1-carbonyl)acrylonitrile (3): A mixture of compound 1 (2.53 g, 0.01 mmoL) and phenyl isothiocyanate (1.35 g, 0.01 mmoL) was stirred overnight in N, N-dimethylformamide in the presence of anhydrous potassium hydroxide (0.84 g, 0.015). The reaction mixture was poured onto ice water then acidified with diluted hydrochloric acid (HCl). The resulting white crystals were filtered and washed with cold water. The filtered product was crystallized from a solution of methanol and diethyl ether.

White crystals; m.p. 277°C; yield 67 %; IR (KBr): ύ cm^{-1} = 3368 (NH), 3132 (=CH of olefinic group), 2223 (CN), 1635 (C=O), 1586 (C=N), 1289 (C=S); ^{1}H-NMR (DMSO-d_6) δ/ppm = 1.62 (s, 1H, SH), 6.24 (s,1H, CH), 7.50-8.20(m, 8H, Ar-H), 10.32(s, 1H, NH). MS: (m/z, %) 390 (M^+ +2, 29%), 254 (25 %), 228 (40%), 159 (31%), 117 (100%), 89 (10%), 63 (23%). Anal. Calcd for $C_{18}H_{11}F_3N_4OS$ (390.0): C, 55.68; H, 2.85; N, 14.43%. Found: C, 55.69; H, 2.83; N, 14.46%.

General procedure for the synthesis of compounds 4, 6, 8, 10 and 12a-c: A mixture of compound 3 (1.95 g, 0.005 mmoL) and α-haloketone or (Z)-2-oxo-N', 2-phenylarylacetohydrazonyl bromide (0.01 mmoL) was stirred in ethanol at room temperature for 6 h. The resulting white crystals were collected by filteration and washed with ethanol. The filtered product was crystallized from a solution of methanol.

(E)-3-(2-oxo-phenylethylthio)-3-(phenylamino)-2-(5-(trifluromethyl)-1H-indazole-1-carbonyl) acrylonitrile (4): White crystals; m.p. 264°C; yield 60%; IR (KBr): ύ cm^{-1} = 3375 (NH), 3130 (=CH of olefinic group), 2253 (CN), 1633, 1640 (two C=O), 1595 (C=C); ^{1}H-NMR ($CDCl_3$) δ/ppm = 3.30 (s, 2H, CH_2), 6.16 (s,1H, CH), 6.52-6.86 (m, 13H, Ar-H), 10.32(s, 1H, NH). MS: (m/z, %) 506 (M^+, 100%), 254 (25%), 398 (46%), 352 (23%), 261 (90%), 249 (16%), 223 (26%), 181 (65%), 153 (54%), 84 (34%). Anal. Calcd for $C_{26}H_{17}F_3N_4O_2S$ (506.3): C, 61.65; H, 3.38; N, 11.06%. Found: C, 61.63; H, 3.39; N, 11.08%.

(E)-3-(cyanomethylthio)-3-(phenylamino)-2-(5-(t r ifluromethyl)-1H-indazole-1-carbonyl)acrylonitrile (6): Yellow crystals; m.p. 281°C; yield 82%; IR (KBr): ύ cm^{-1} = 3329 (NH), 3089 (=CH of olefinic group), 2250, 2223 (two CN), 1642, 1640 (two C=O), 1610 (C=C); ^{1}H-NMR ($CDCl_3$) δ/ppm = 4.30 (s, 2H, CH_2), 5.30 (s, 1H,NH), 6.12 (s, 1H, CH), 6.54 (s, 1H, CH), 6.78 (d, 1H, CH), 6.94 (d, 1H, CH),7.10-7.90 (m, 5H, Ar-H). MS: (m/z, %) 428 (M^+ +1, 50%), 402 (75%), 333 (41%), 287 (26%), 196 (91%), 184 (18%), 118 (32%), 90 (25%), 77 (100%), 66 (34%). Anal. Calcd for $C_{20}H_{12}F_3N_5OS$ (428): C, 56.20; H, 2.83; N, 16.39%. Found: C, 56.22; H, 2.84; N, 16.36%.

(E)-3-(2-oxopropylthio)-3-(phenylamino)-2-(5-(tri fluromethyl)-1H-indazole-1-carbonyl)acrylonitrile (8): Pale yellow powder; m.p. 276°C; Yield 52%; IR (KBr): ύ cm^{-1} = 3444 (NH), 3069 (=CH of olefinic group), 2230 (CN), 1731, 1635 (two C=O), 1625 (C=C); ^{1}H-NMR ($CDCl_3$) δ/ppm = 2.33 (s, 3H, CH_3), 4.20 (s,1H,NH), 4.22 (s, 2H, CH_2), 6.11 (s, 1H, CH), 6.64 (s,1H, CH), 6.78 (d, 1H, CH), 6.74 (d, 1H, CH),7.20-7.60 (m, 5H, Ar-H). MS: (m/z, %) 444 (M^+ , 56%), 375 (100%), 349 (46%), 334 (39%), 292 (71%), 260 (28%), 145 (32%), 117 (25%), 89 (14%), 77 (34%). Anal. Calcd for $C_{21}H_{15}F_3N_4O_2S$ (444): C, 56.75; H, 3.40; N, 12.61%. Found: C, 56.72; H, 3.43; N, 12.59%.

(E)-ethyl2-(2-cyano-3-oxo-1-(phenylamino)-3-(5-tri fluoromethyl)-1H-indazol-1-yl)prop-1-enylthio) acetate (10): Brown powder; m.p. 261°C; Yield 59%; IR (KBr): ύ cm^{-1} = 3422 (NH), 3086 (=CH of olefinic group), 2220 (CN), 1730, 1636 (two C=O), 1617 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 1.20 (t, 3H, CH_3), 3.70

(q, 2H, CH_2),4.24 (s, 2H, CH_2), 6.89-7.11 (m, 9H, Ar-H), 8.40 (s, 1H,NH). MS: (m/z, %) 476 (M^++2, 44%), 407 (16%), 316 (46%), 243 (19%), 197 (51%), 131 (100%), 103 (33%), 89 (74%), 77 (39%). Anal. Calcd for $C_{22}H_{17}F_3N_4O_3S$ (476): C, 55.69; H, 3.61; N, 12.81%. Found: C, 55.72; H, 3.63; N, 12.79%.

(E)-2-cyano-3-oxo-1-(phenylamino)-3-(5-(trifluoromethyl)-1H-indazol-1-yl)prop-1-enyl-2-oxo-N-2-diphenylethane hydrazonothioate (12a): White crystal; m.p. 264°C; Yield 76%; IR (KBr): ύ cm^{-1} = 3422 (NH), 3086 (=CH of olefinic group), 2221 (CN), 1690, 1636 (two C=O), 1615 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 6.24 (s, 1H, CH), 6.51 (s, 1H, NH), 6.80-7.19 (m, 18H, Ar-H), 8.42 (s, 1H,NH). MS: (m/z, %) 610 (M , 34%), 507 (57%), 430 (69%), 402 (39%), 358 (58%), 255 (70%), 205 (43%), 163 (71%), 137 (100%), 68 (14%). Anal. Calcd for $C_{32}H_{21}F_3N_6O_2S$ (610): C, 62.94; H, 3.47; N, 13.76%. Found: C, 62.95; H, 3.43; N, 13.79%.

(E)-2-cyano-3-oxo-1-(phenylamino)-3-(5-(trifluoromethyl)-1H-indazol-1-yl)prop-1-enyl-2-oxo-N',2-p-tolylphenylethane hydrazonothioate (12b): Buff crystal; m.p. 274°C; Yield 56%; IR (KBr): ύ cm^{-1} = 3387 (NH), 3125 (=CH of olefinic group), 2232 (CN), 1675, 1640 (two C=O), 1599 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 2.31 (s, 3H, CH_3), 6.24 (s, 1H, CH), 6.56 (s, 1H, NH), 6.80-7.19 (m, 17H, Ar-H), 9.72 (s,1H,NH). MS: (m/z, %) 624 (M^+, 26%), 520 (87%), 494 (57%), 479 (39%), 404 (18%), 376 (10%), 332 (94%), 229 (46%), 191 (10%), 163 (100%),135 (14%), 123 (52%), 54 (26%). Anal. Calcd for $C_{27}H_{18}F_3N_5O_2S$ (533): C, 60.78; H, 3.40; N, 13.13%. Found: C, 60.75; H, 3.43; N, 13.10%.

(E)-2-cyano-3-oxo-1-(phenylamino)-3-(5-(trifluoromethyl)-1H-indazol-1-yl)prop-1-enyl-2-oxo-N', 2-(p-methoxyphenyl)phenylethane hydrazonothioate (12c): Buff crystal; m.p. 271°C; Yield 56%; IR (Kbr): ύ cm^{-1} = 3364 (NH), 3123 (=CH of olefinic group), 2242 (CN), 1682, 1643 (two C = O), 1607 (C = C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 3.41 (s, 3H, OCH_3), 6.34 (s,1H, CH), 6.67 (s, 1H, NH), 6.74 (d, 1H, 2 CH), 6.79 (d,1H, 2 CH), 7.40-7.29 (m, 13H, Ar-H), 9.11 (s,1H,NH). MS: (m/z,%) 640 (M^+, 26%), 609 (80%), 583 (52%), 479 (35%), 405 (28%), 376 (10%), 331 (58%), 228 (71%), 191 (16%), 162 (100%), 135 (24%), 123 (52%), 54 (22%). Anal. Calcd for $C_{33}H_{23}F_3N_6O_3S$ (640): C, 61.87; H, 3.62; N, 13.13%. Found: C, 61.85; H, 3.65; N, 13.11%.

General procedure for synthesis compounds 5, 7, 9, 11 and 13a-c

Pathway 1: A mixture of compound 3 (1.95 g, 0.005 mmoL) and α-haloketone or (Z)-2-oxo-N', 2-phenylarylacetohydrazonyl bromide (0.01 mmol) was heated under reflux for 4 hr in N,N-dimethylformamide (DMF) containing a catalytic amount of triethylamine. The reaction mixture was poured onto cold water then acidified by dil. HCl. The precipitate was collected by filtration then dried and recrystallized from ethanol to give the targeted compounds.

Pathway 2: A solution of compounds 4, 6, 8, 10 and 12a-c in DMF was refluxed for about 3 h in presence of few drops of triethylamine. The reaction mixture was poured onto cold water then acidified by dil. HCl. The precipitate was collected by filteration then dried and recrystallized from ethanol to give the targeted compounds.

3-amino-5-(phenylamino)-4-(5-(trifluoromethyl)-1H-indazole-1-carbonyl)thiophen-2-yl)phenylmethanone (5): Brown crystal; m.p. 264°C; Yield 42%; IR (KBr): ύ cm^{-1} = 3438, 3429 (NH_2), 3158 (NH), 3123 (=CH of olefinic group), 1633, 1662 (two C=O), 1599 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 6.21 (s, 1H, NH_2), 7.40-8.00 (m, 13H, Ar-H), 9.00 (s, 1H,NH). MS: (m/z, %) 506 (M^+, 25%), 437 (58%), 398 (46%), 405 (24%), 289 (12%), 261 (16%), 158 (55%), 118 (100%), 90 (56%), 66 (34%). Anal. Calcd. for $C_{26}H_{17}F_3N_4O_2S$ (506.3): C, 61.66; H, 3.37; N, 11.05%. Found: C, 61.63; H, 3.36; N, 11.06%.

3-amino-5-(phenylamino)-4-(5-(trifluoromethyl)-1H-indazole-1-carbonyl)thiophen-2-carbonitrile (7): Pink crystal; m.p. 281°C; Yield 42%; IR (KBr): ύ cm^{-1} = 3437, 3421 (NH_2), 3228 (NH), 3196 (=CH of olefinic group), 2245 (CN), 1665 (C=O), 1600 (C=C); ^{1}H-NMR (DMSO-d_6) |/ppm = 6.32 (s, 1H, NH_2), 7.40-8.00 (m, 9H, Ar-H), 10.02 (s, 1H,NH). MS: (m/z,%) 429 (M^++2, 50%), 403 (48%), 312 (91%), 296 (36%), 216 (74%), 188 (100%), 160 (32%), 91 (25%), 67 (64%). Anal. Calcd. for $C_{20}H_{12}F_3N_5OS$ (428.1): C, 56.21; H, 2.84; N, 16.39%. Found: C, 56.23; H, 2.86; N, 16.37%.

1-(3-amino-5-(phenylamino)-4-(5-(trifluoromethyl)-1H-indazole-1-carbonyl)thiophen-2-yl) ethanone (9): Pale red powder; m.p. 256 °C; Yield 52%; IR (KBr): ύ cm^{-1} = 3444, 3423 (NH_2), 3261 (NH), 3202 (=CH of olefinic group), 1701, 1662 (two C=O), 1605 (C=C); ^{1}H-NMR ($CDCl_3$) δ/ppm = 2.13 (s, 3H, CH_3), 6.21 (s, 1H, CH), 6.67 (s, 1H, CH), 6.73 (d, 1H, CH), 6.74 (d, 1H, CH), 7.00-7.34 (m, 5H, Ar-H), 7.95 (s, 1H,NH). MS: (m/z,%) 444 (M^+, 100%), 375 (10%), 332 (32%), 316 (79%), 236 (53%), 208 (68%), 180 (39%), 117 (25%), 89 (14%), 168 (34%), 99 (60%). Anal. Calcd. for $C_{21}H_{15}F_3N_4O_2S$ (444): C, 56.76; H, 3.41; N, 12.62%. Found: C, 56.72; H, 3.40; N, 12.60%.

Ethyl 3-amino-5-(phenylamino)-4-(5-(trifluoromethyl)-1H-indazole-1-carbonyl)thiophen-2-carboxylate (11): Brown powder; m.p. 276°C; Yield 39%; IR (KBr): ύ cm^{-1} = 3422, 3389 (NH_2), 3275 (NH),

3086 (=CH of olefinic group), 1732, 1656 (two C=O), 1614 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 1.23 (t,3H, CH_3), 3.76 (q, 2H, CH_2), 6.57 (s, 2H, NH_2), 6.89-7.11 (m,9H, Ar-H), 9.43 (s, 1H,NH). MS: (m/z,%) 475 (M^++1, 88%), 406 (16%), 333 (46%), 242 (39%), 226 (56%), 146 (46%), 118 (11%), 90 (100%), 65 (19%). Anal. Calcd for $C_{22}H_{17}F_3N_4O_3S$ (474.2): C, 55.70; H, 3.62; N, 12.82%. Found: C, 55.72; H, 3.60; N, 12.80%.

2-(5-benzoyl-3-phenyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)-3-oxo-3-(5-(trifluoromethyl)-1H-indazol-1-yl)propane-nitrile (13a): Yellow powder; m.p. 250°C; Yield 76%; IR (KBr): ύ cm^{-1} = 3226 (NH), 3085 (=CH of olefinic group), 2231 (CN), 1652, 1636 (two C=O), 1610 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 6.24 (s,1H, CH), 6.72 (s, 1H, NH), 6.81-7.19 (m, 13H, Ar-H), 8.45 (s, 1H,NH). MS: (m/z,%) 521 (M^++2, 14%), 417 (97%), 341 (61%), 315 (31%), 251 (70%), 239 (100%), 211 (46%), 142 (100%), 114 (14%). Anal. Calcd. for $C_{26}H_{16}F_3N_5O_2S$ (519.3): C, 60.11 ; H, 3.10 ; N, 13.48%. Found: C, 60.10; H, 3.13; N, 13.49%.

2-(5-benzoyl-3-p-tolyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)-3-oxo-3-(5-(trifluoromethyl)-1H-indazol-1-yl)propane-nitrile (13b): Bege crystals; m.p. 265°C; Yield 76%; IR (KBr): ύ cm^{-1} = 3229 (NH), 3086 (=CH of olefinic group), 2232 (CN), 1672, 1646 (two C=O), 1612 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 2.31 (s,3H, CH_3), 6.64 (s, 1H, CH), 6.70 (s, 1H, NH), 6.76-6.95 (m, 12H, Ar-H), 9.99 (s, 1H,NH). MS: (m/z,%) 533 (M^+,18%), 442 (97%), 338 (41%), 312 (38%), 248 (63%), 236 (58%), 208 (100%), 139 (46%), 111 (14%), 99 (92%). Anal. Calcd. for $C_{27}H_{18}F_3N_5O_2S$ (533.3): C, 60.78 ; H, 3.40; N, 13.13%. Found: C, 60.79 ; H, 3.43; N, 13.16%.

2-(5-benzoyl-3-(4-methoxyphenyl)-2, 3-dihydro-1,3,4-thiadiazol-2-yl)-3-oxo-3-(5-(trifluoromethyl)-1H-indazol-1-yl)propane-nitrile (13c): White crystals; m.p. 284°C; Yield 76%; IR (KBr): ύ cm^{-1} = 3229 (NH), 3086 (=CH of olefinic group), 2232 (CN), 1672, 1646 (two C=O), 1612 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 4.01 (s, 3H, OCH_3), 6.14 (s, 1H, CH), 6.39 (s,1H, NH), 6.46-6.99 (m, 12H, Ar-H), 10.10 (s, 1H, NH). MS: (*m/z*,%) 549 (M^+, 68%), 442 (45%), 388 (31%), 312 (50%), 228 (63%), 188 (58%), 119 (100%), 91 (46%), 79 (14%), 67 (92%). Anal. Calcd. for $C_{27}H_{18}F_3N_5O_3S$ (549.3): C, 59.01 ; H, 3.30 ; N, 12.74%. Found: C, 59.03 ; H, 3.33; N, 12.76%.

3-amino-5-(phenylamino)-1H-pyrazol-4-yl-(5-(trifluoromethyl)-1H-indazol-1-yl)methane (15): A mixture of compound 3 (1.95 g, 0.005 mmoL) and hydrazine hydrate (0.5 g, 0.01 mmoL) was heated under reflux for 4 h in DMF and ethanol. The reaction mixture was poured onto cold water then acidified by dil. HCl. The precipitate was collected by filtration then dried and recrystallized from ethanol to give the targeted compounds.

Yellow powder; m.p. 255°C; Yield 46%; IR (KBr): ύ cm^{-1} = 3444, 3421 (NH_2), 3320, 3226 (two NH), 3086 (=CH of olefinic group), 1651 (C=O), 1616 (C=C); ^{1}H-NMR (DMSO-d_6) δ/ppm = 6.34 (s, 1H, CH), 5.32 (s, 2H, NH_2), 6.73 (s, 1H, NH), 6.89-7.23 (m, 13H, Ar-H), 8.49 (s, 1H,NH). MS: (m/z,%) 386 (M^+, 74%), 295 (100%), 279 (60%), 215 (36%), 187 (60%), 118 (17%), 90 (46%), 66 (70%). Anal. Calcd. for $C_{18}H_{13}F_3N6_5O$ (386.2): C, 55.96 ; H, 3.39 ; N, 21.75%. Found: C, 55.97; H, 3.40; N, 21.76%.

Pharmacology

Antidepressant activity: Local breed, male albino mice (20-24 g) were used in the forced swimming test under standard conditions with free access to food and water. They were housed in groups of six. On test day mice were dropped one at a time into a plexiglass cylinder (height 25 cm, diameter 10 cm) containing 10 cm of water at 23-25°C (Porsolt *et al*., 1977, 1981). On the testing day, mice were assigned into different groups (n= 6-9 for each group).

Statistical analysis: Results are expressed as Mean±SEM; n represents the number of animals. Data obtained from pharmacological experiments were analyzed by one way analysis of variance (ANOVA) followed by Dunnet's post hoc test and used to evaluate the results, employing pharmacologic calculation system version 4.1. (Microcomputer Specialists). A p-value of less than 0.05 was considered statistically significant.

Antifungi: The disks of Whatman filter paper were prepared with standard size (5.0 mm diameter) and kept into 1.0 Oz screw capped wide mouthed containers for sterilization. These bottles are kept into hot air oven at temperature of 150°C. Then, the standard sterilized filter paper disks impregnated with a solution of the test compound in DMF (1 mg mL^{-1}) were placed on nutrient agar plate seeded with the appropriate test organism in triplicates (Fadda *et al*., 2013).

Minimal inhibitory concentration (MIC) measure: The microdilution susceptibility test in Müller-Hinton Broth and Sabouraud Liquid Medium were used for the determination of antifungal activity, respectively. Each stock solution was diluted with standard method broth to prepare serial two fold dilutions in the range of 500-3.125 mg mL^{-1} 10 mL of the broth containing about 10^6CFU mL^{-1} of test bacteria was added to each well of 96-well microtiter plate (Fadda *et al*., 2013).

RESULTS AND DISCUSSION

New generation of thiophenes: As a part of reported research on drug discovery program (Fadda *et al*., 2008,

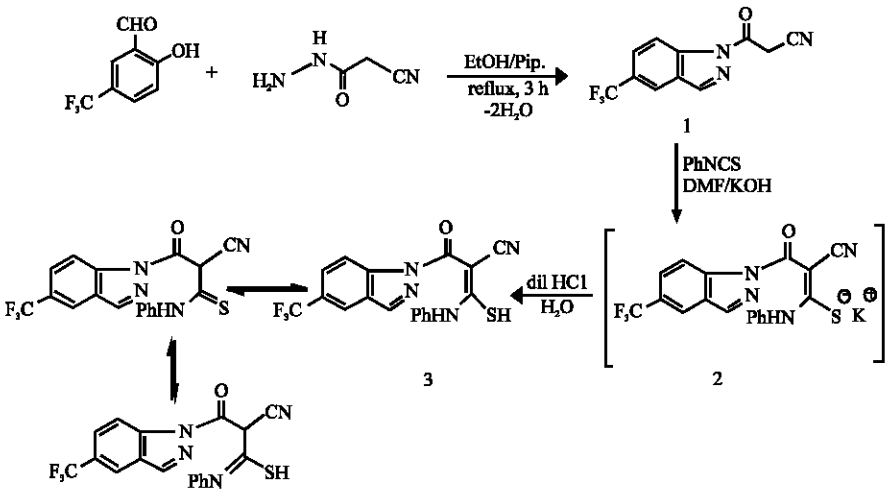

Fig. 1: Synthesis of thicarbamoyl derivative 3

2009, 2012), we needed to describe facile and rapid procedure for construction of drug like small organic molecules using various reagents. Firstly, the acidic methylene compound 1 was formed by condensation reaction of 2-hydroxy-5-(trifluoromethyl) benzaldehyde with 2-cyano acetochydrazide in refluxing ethanol in the presence of a catalytic amount of pipridine for 3 h. Thus, the base catalyzed reaction of compound 1 with phenyl isothiocyanate in dry N,N-dimethylformamide in the presence of potassium hydroxide at room temperature led to the formation of the non-isolable intermediate 2 which gave thiocarbamoyl derivative 3 in three tautomeric structures upon treatment with diluted HCl (Fig. 1).

Assignment of compound 3 was based on elemental analysis, IR and ^{1}H-NMR spectral data. The IR spectrum showed absorption bands at 3368, 2223 and 1289 cm^{-1} attributable to the NH, CN and C=S functions, respectively. Nuclear magnetic resonance of hydrogen nuclei (^{1}H-NMR) spectra of 3 displayed a singlet signal at δ 1.62 corresponding to SH proton. It also showed multiplet signals at δ 7.50-8.20 ppm for aromatic protons and a singlet signal at δ 10.32 ppm for NH proton. Its mass spectrum showed molecular ion peak m/z = 390 (M^++2, 23%) corresponding to the molecular formula $C_{18}H_{11}F_3N_4OS$.

On the other hand, compound 3 also undergoes cyclization upon the reaction with equimolar amounts of phenacyl bromide in boiling N,N-dimethylformamide and in presence of catalytic amount of triethylamine yielded a product 5, which was analyzed correctly for $C_{26}H_{17}F_3N_4O_2S$. The structure 5 was inferred from its spectral data. Thus, the IR spectrum showed absorption bands at 3438, 3429, 3158, 1662, 1633 and 1599 cm^{-1} corresponding to NH_2, NH, two CO and C=C functions, respectively. Its ^{1}H-NMR spectrum showed two singlet signals at δ 9.00 and 6.21 ppm corresponding to NH and NH_2 protons, respectively and multiplet signals integrated for (13H) centered at 7.40 and 8.00 ppm (aromatic protons). On shaking the compound with D_2O, the broad band signals at δ 9.00 and 6.21 ppm disappeared. Moreover, structure 5 was confirmed by its mass spectrum which showed the molecular ion peak at m/z = 506 (M^+, 79%) corresponding to the molecular formula $C_{26}H_{17}F_3N_4O_2S$. Based on the forgoing data, structure 5 was assigned to this product. The structure 5 was further proved by alternative synthesis. Thus, it was found that, stirring of 2 with phenacyl bromide in ethanol at room temperature afforded the acyclic intermediate 4 by hydrogen bromide (HBr) elimination. Structure 4 was suggested for the reaction product on the basis of both elemental and spectral analyses. The IR spectrum showed absorption bands at 3375, 2253, 1633, 1640 and 1595 cm^{-1} corresponding to NH, CN, two CO and C=C functions, respectively.

Refluxing of compound 4 in N, N-dimethyl formamide with few drops of triethylamine led to the formation of a product identical in all respects (m.p., mixed m.p. and IR) to 5 (Fig. 2).

Similarly, when the intermediate potassium salt 2 was stirred with chloroacetonitrile in ethanol at room temperature, the corresponding acyclic intermediate 6 is exclusively isolated in good yield. The structure of 6 has been confirmed on the basis of elemental and spectral data. The IR spectrum exhibits bands at 3329 (NH), 2250, 2223 (two CN), 1642 (CO) and 1610 cm^{-1} (C=C). Its ^{1}H-NMR spectrum reveals a singlet signals at δ 4.30 ppm corresponding to CH_2 protons, multiplet signals at δ 7.10-7.90 ppm for aromatic protons and singlet signal at δ 5.30 corresponding to NH proton. Furthermore,

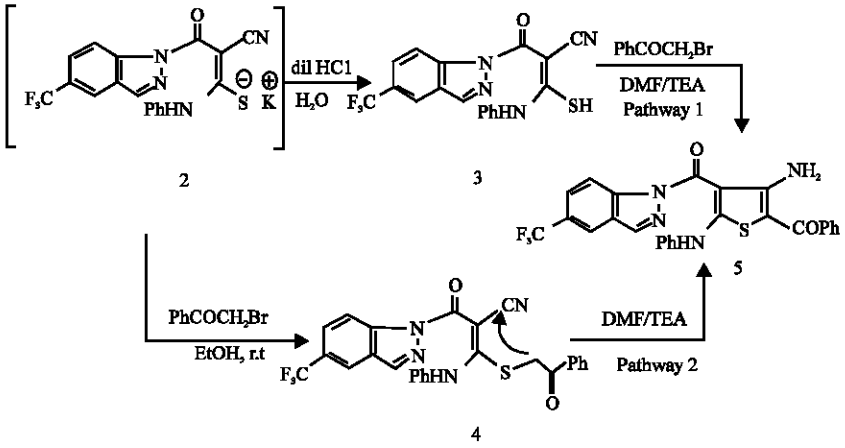

Fig. 2: Alternative synthesis of thiophene derivative 3

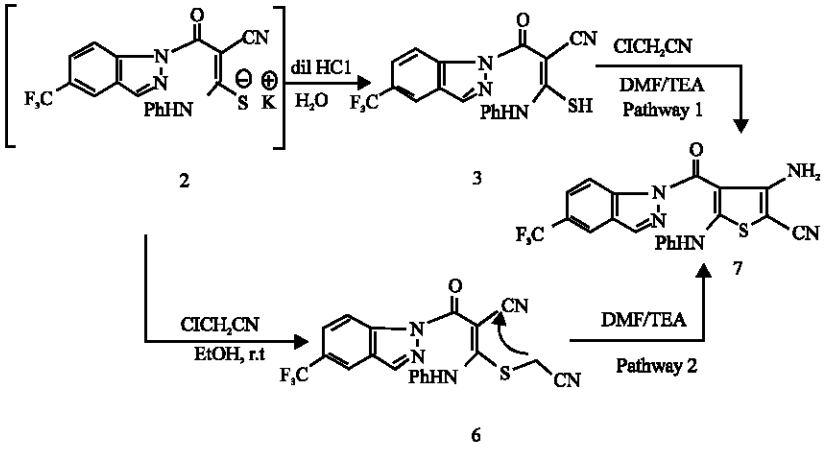

Fig. 3: Synthesis of thiophene derivative 7

refluxing of the acyclic intermediate 6 in N, N-dimethylformamide containing a catalytic amount of triethylamine afforded the thiophene derivative 7. The thiophene derivative 7 was established based on its elemental and spectral analyses (see experimental section). On the other hand, it has been found that compound 7 is directly formed by refluxing compound 3 with chloroacetonitrile in N,N-dimethylformamide and in presence of catalytic amount of triethylamine by pathway (1) (Fig. 3).

In order to extend the utility of thiocarbamoyl derivative 3 as a building block for preparation of sulfur-containing heterocycles, compound 2 reacted readily with chloroacetone in the presence of ethanol at room temperature to afford the acyclic intermediate 8 by potassium chloride (KCl) elimination. The acyclic intermediate 8 was established based on its IR spectrum which showed bands at 3444, 2230, 1635, 1731 and 1625 cm^{-1} corresponding to NH, CN, two CO and C=C function groups, respectively. Its ^{1}H-NMR spectrum revealed three singlet signals at δ 2.33, 4.22. 4.20 ppm for CH_3, CH_2 and NH protons, respectively. Also, its ^{1}H-NMR spectrum showed multiplet signals at δ 7.20-7.60 ppm for aromatic protons.

Refluxing of compound 8 in ethanol in N,N-dimethylformamide in presence of catalytic amount of triethylamine gave the thiophene derivative 9 whose structure was confirmed by its alternative synthesis. Also, refluxing of compound 3 with chloroacetone in N,N-dimethylformamide in presence of catalytic amount of triethylamine afforded the thiophene derivative 9 in reasonably good yield (Fig. 4).

The ^{1}H-NMR spectrum of the thiophene derivative 9 reveals two characteristic singlet signals at δ 2.13 and 7.95 ppm due to CH_3 and NH protons.

Classically, when the compound 3 was treated with an equimolar amount of ethyl chloroacetate, with ethyl bromoacetate, with chloroacetic acid or with chloroacetyl chloride in mixture of N,N-dimethylformamide and ethanol in presence of a catalytic

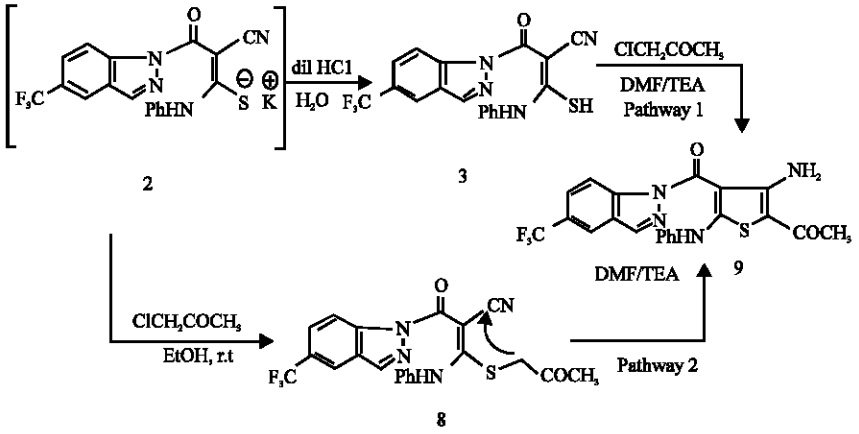

Fig. 4: Utility of chloroacetyl chloride in synthesis of thiophene derivative 9

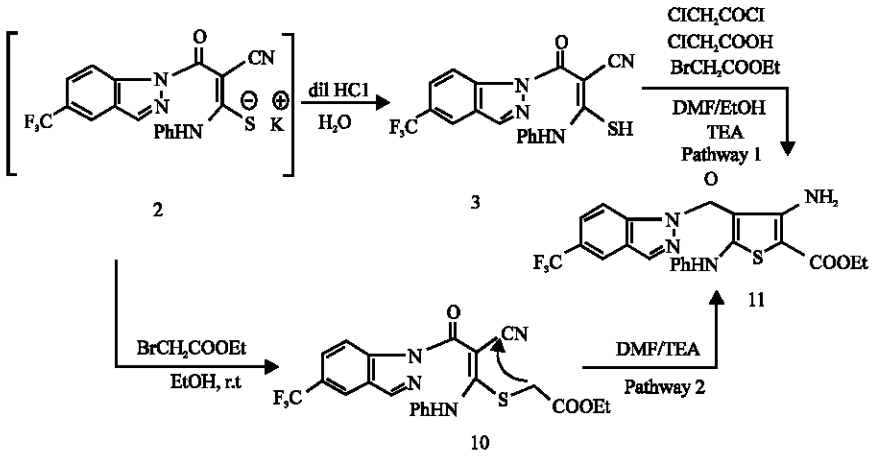

Fig. 5: Different reagents used for synthesis of thiophene derivative 11

amount of triethylamine, product 11 analyzed for $C_{22}H_{17}F_3N_4O_3S$ was isolated in each case in good yield. Moreover, the reaction of the intermediate 2 with an equimolar amount of ethyl chloroacetate, with ethyl bromoacetate or with chloroacetic acid in ethanol led to the formation of compound 10. The acyclic structure 10 was established based on its IR spectrum that showed absorption bands at 3422, 2220, 1636, 1730 and 1617 cm^{-1} attributable to the NH, CN, two CO and C=C functions, respectively. Its ^{1}H-NMR spectrum reveals a triplet signal at δ 1.20 (3H, CH_3), quartet at δ 3.70 (2H, CH_2) and a D_2O exchangeable NH at δ 8.40 ppm. The structure of 10 was confirmed by its mass spectrum which showed a peak at m/z = 476 (M^++2, 39%). Refluxing of 10 in N,N-dimethylformamide with a catalytic amount of triethylamine afforded the corresponding thiophene derivative 11. In similar manner, the thiophene derivative 11 was prepared by pathway (1) as outlined in (Fig. 5).

Interestingly, refluxing of compound 3 with various (Z)-2-oxo-N', 2-phenylarylacetohydrazonyl bromide derivatives in N,N-dimethylformamide in presence of catalytic amount of triethylamine afforded thiophene product 13a-c. Alternatively, compound 13a-c was synthesized by refluxing the acyclic intermediate 12a-c in amixture of solvent from N,N-dimethylformamide and ethanol in presence of catalytic amount of triethylamine. Furthermore, the non-isolable intermediate 2a-c was stirred with an equimolar amount (Z)-2-oxo-N', 2-phenylarylacetohydrazonyl bromide in absolute ethanol. The acyclic structures 12a-c were established based on their IR spectrum that showed absorption bands at 3422-3321, 3311-3289, 2251-2221, 1690-1636 and 1617-1598 cm^{-1} attributable to the two NH, CN, two CO and C=C functions, respectively. Its ^{1}H-NMR spectrum reveals a singlet signals at δ 9.10-8.33 ppm due to a D_2O exchangeable two NH in each compound (Fig. 6).

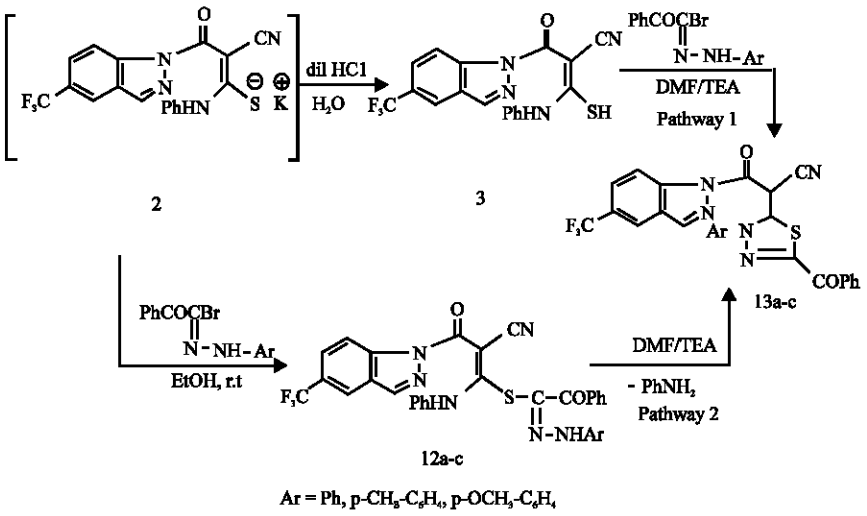

Fig. 6: New generation of thiadiazole derivatives 13a-c

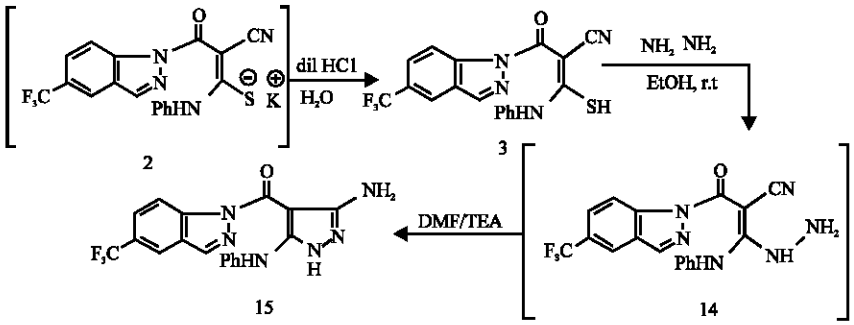

Fig. 7: Formation of newly pyrazole ring

Synthesis of novel pyrazole ring: In the course of these studies on synthesis of heterocycles using thiocarbamoyl derivative 3, it has been found that a one-step method for synthesizing compound 15 from thiocarbamoyl derivative 3. Successfully, treatment of the compound 3 with hydrazine hydrate in N,N-dimethylformamide and ethanol in the presence of a catalytic amount of triethylamine gave structure 15. The formation of compound 15 is assumed to proceed via the replacement of the SH group by the hydrazine moiety to give the non-isolable intermediate 14. In fact, the structure of 15 was further confirmed by both elemental and spectral analyses. The IR spectrum of compound 15 showed no absorption band at 2251 cm^{-1} and this is attributable to the consumption of cyano group in the reaction and appearance of an absorption bands at 3444-3421 (NH_2), 3320, 3226 (two NH), 1652 (CO) and 1610 cm^{-1} (C=C) function groups. The ^{1}H-NMR spectrum revealed a broad signal at δ 6.68 ppm assigned for NH_2 protons, a multiplet at δ 7.2-7.8 ppm for aromatic protons and a singlet signal at δ 10.71 and 11.00 ppm for two NH protons (Fig. 7).

Biological implementation

Antidepressants: Antidepressants are psychiatric medications given to patients with depressive disorders to alleviate symptoms. They correct chemical imbalances of neurotransmitters in the brain which probably cause changes in mood and behavior. Antidepressants may be used for a wide range of psychiatric conditions, including social anxiety disorder, anxiety disorders and dysthymia (mild chronic depression). Antidepressants were initially developed in the 1950s and have become progressively more common over the last twenty years. In 1996, there were 13.3 million people using antidepressants in the United States; this figure jumped to 27 million in 2005, an increase of over 100%. Researchers from Columbia University Medical Center, the New York State Psychiatric Institute and the University of Pennsylvania added that rates remained low among racial and ethnic

Table 1: *In vitro* antidepressant activity of the synthesized compounds

		Antidepressant activities	
Entry	Compd No.	Duration of immobility (sec) (Mean±SEM)	Change from control (%)
1	1	223±4.5	2.46
2	3	221±9.8	5.81
3	4	209±17.3	12.38
4	5	149±11.35	-15.78
5	6	201±16.4	-11.25
6	7	142±10.85	-21.97
7	8	205±18.0	-2.69
8	9	182±7.8	-32.45
9	10	201±22.3	0.56
10	11	122±7.9	-55.14
11	12a	193±9.7	-13.45
12	12b	199±17.3	-8.85
13	12c	200±9.8	-13.40
14	13a	105±6.5 193	-31.56
15	13b	112±6.9	-64.85
16	13c	117±7.1	-69.25
17	15	192±12.9	-13.81
18	Tranylcypromine sulfate (10 mg kg^{-1}, ip)	57±11.6	-72.85
19	Control	210±7.3	-

Values represent the Mean±SEM, (n = 6), *Significantly compared to control (Dunnet's test, $p<0.05$)

Table 2: Minimal inhibitory concentration (MIC, $\mu g\ mL^{-1}$) of some new synthesized compounds

		[a]MIC in $\mu g\ mL^{-1}$ Inhibition diameter (mm)		
Entry	Compd No.	*Spergillusflavus*	*F. oxysporum*	*B. fabae*
1	5	[b]NT	50.0 (19)	25.0 (27)
2	7	12.5 (28)	25.0 (27)	12.5 (26)
3	9	25 (30)	12.5 (14)	50.0 (15)
4	11	6.25 (39)	6.25 (41)	6.25 (40)
5	13a	3.125 (44)	3.125 (44)	3.125 (32)
6	13b	3.125 (44)	3.125 (45)	6.25 (38)
7	13c	3.125 (44)	3.125 (44)	3.125 (36)
8	Cycloheximide	3.125(42)	3.125 (43)	3.125 (42)

[a]MIC: Minimal inhibitory concentration values with SEM = 0.02, [b]NT: Not tested

minorities. They believe that antidepressant usage has become more common because:

- There has been a broadening in the concepts of need for mental health treatment
- Campaigns to promote mental health care have become more widespread
- Mental health treatments have become more widely accepted by the public

According to data gathered from public health authorities in Canada, Western Europe and Australasia, increased antidepressant usage has been a progressively common trend in most industrialized countries. As a result, the synthesized compounds 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12a-c, 13a-c and 15 were tested as antidepressant. The forced swimming test is a behavioural test used to predict the efficacy of antidepressant treatments (Porsolt *et al*., 1977). It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and atypical antidepressants (Porsolt, 1981). It has a good predictive value for antidepressant potency in humans (Willner and Mitchell, 2002). The obtained data on the antidepressant activity of the compounds and reference drug are given in Table 1. In this study, Compounds 13a-c significantly reduced the duration of immobility times at 10 mg kg^{-1} dose level when compared to control ($p<0.05$, Table 1) while compounds 11, 7, 5, 9, 15 exhibit moderat activity than the rest of compound comparing to control.

Traditionally, many invasive fungal infections were associated with a poor prognosis because effective therapeutic options were limited. The recent development of new antifungal agents has significantly contributed to the successful treatment of fungal diseases. These drugs offered novel mechanisms of action and expanded spectrums of activity over traditional treatment options. However, with these new agents comes the need for increased awareness of the potential interactions and toxicities associated with these drugs. Therefore, an understanding of the pharmacokinetic and pharmacodynamic properties of the classes of antifungal compounds is vital for the effective management of invasive fungal infections. This article provides novel drugs of the pharmacologic interest involved in treatment of fungal diseases. Agar-diffusion method was used for the determination of the antifungal activity *Spergillus flavus*, *Fusarium oxysporum* and *Botrytis fabae*. Cycloheximide were used as reference drugs. The results were recorded for each tested compound as the average diameter of Inhibition Zones (IZ) of bacterial or fungal growth around the disks in mm. The Minimum Inhibitory Concentration (MIC) measurement was determined for compounds that showed significant growth inhibition zones (<14 mm) using two fold serial dilution method (Fadda *et al*., 2013). The MIC ($\mu g\ mL^{-1}$) and inhibition zone diameters values are recorded in Table 2.

Concerning the antifungal activity of the compounds 5, 7, 9, 11 and 13a-c, 13a-c exhibited a broad spectrum of antifungal profile against the tested organisms (MIC 3.125 $\mu g\ mL^{-1}$) comparing to a control drug. The fungal strain which screened for the compound 11 exhibited good activity (MIC 6.25 $\mu g\ mL^{-1}$) whereas compounds 7, 5 and 9 showed moderate to lower activity (MIC 12.5-100 $\mu g\ mL^{-1}$).

Regarding to the structure activity relationship, the substituted pattern was also crucial. It is worth mentioning that compounds 13a-c showed significant activity, respectively as antidepressant and antifungi. This may be attributable to the thiadiazole ring which contains substituents having lower electron donating

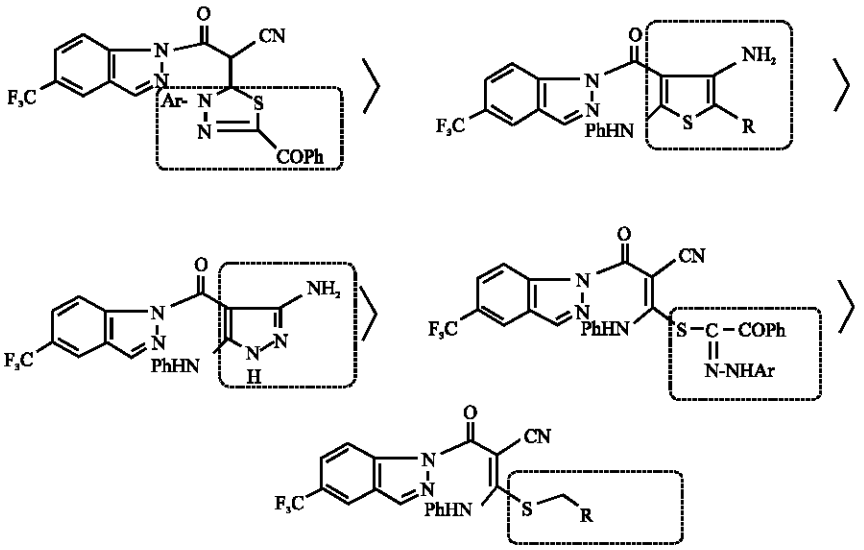

Fig. 8: Different effected circumscribed moieties in biological implementations

group in order 13a>13b>13c. The results showed that compounds possess a large number of rings incorporating large number of heteroatoms especially sulfur atom because of its priority (high group number) and less electronegativity (high acidity) revealed more potency. Also, thiophene ring showed a more moderate activity than pyrazole ring itself. So, the trend of activity is as follows: 13a>13b>13c>11>7>5>9>15>12a>12b>12c>10>6>4>8>3>1 (Fig. 8).

CONCLUSION

The main objective is to synthesize and investigate new heterocycles with hope of discovering new structures serving as antidepressant and antifungi. According to the biological evaluations, tested compounds showed high to weak significant antidepressant and antifungi effects. Compounds 13a-c possess good antidepressant activities due to the presence of thiadiazole ring . The rest of synthesized compounds could be considered as valuable templates for further modification or derivatization to design more potent antidepressant agents. From the above results, one can establish that the synthesized substituted thiophenes, pyrazole and thiadiazoles can be a rich source for the exploitation. All compounds were confirmed by IR, ^{1}H-NMR and mass spectroscopy.

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