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Research Article
Analgesic, Anticonvulsant and Antiparkinsonian Activities of Some Synthesized 2,6-bis(Tetracarboxamide)-pyridine and Macrocyclic Tripeptide Derivatives

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Abstract
A series of synthesized 2,6-bis(tetracarboxamide)-pyridine and macrocyclic tripeptide derivatives 1-6 were previously prepared and screened as antimicrobial, anti-inflammatory and anticancer agents. The compounds for evaluation of analgesic, anticonvulsant and antiparkinsonian activities were used. Analgesic activities of selected compounds determined by hot plate assay, all tested compounds showed this property. Anticonvulsant activities of selected compounds measured their abilities to antagonize yohimbine-induced clonic seizure, all tested compounds showed this property. The antiparkinsonian activity measured by the ability of compounds to protect animals against the parkinsonian like signs induced by agonists, all tested compounds showed this property. All tested compounds showed analgesic, antipakinsonian and anticonvulsant activities and the order for these activities were 5b, 6a, 3, 5a, 5c, 4, 6c, 2, 6b and 1.

Key words: 2,6-substituted pyridine, macrocyclic tripeptide, pharmacological activities

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

In previous study it is reported that certain substituted pyridines and their chiral macrocyclic derivatives have biological and pharmacological activities such as; antimicrobial (Abd El-Salam *et al*., 2012; Amr *et al*.,1999, 2003a, 2006a; Al-Salahi *et al*., 2010), anticancer (Abo-Ghalia and Amr, 2005; Amr *et al*., 2006b), analgesic and anticonvulsant (Amr, 2005; Abd El-Latif *et al*., 2007) activities. The heterocyclic derivatives have effective biological importance. For example, a large number of nitrogen atoms are interesting drug candidates including anti-inflammatory, antianxiety, antimicrobial agents and antimycotic activity (Sahu *et al*., 2014; Holla *et al*., 1994). Branched-chain amino acid mixture has been used for treatment of hypoalbuminemia in patients with decompensated liver cirrhosis (Nishitani *et al*., 2004).

Nishitani *et al*. (2002) found a novel pharmacological effect of leucine in skeletal muscle. In view of these observations and in continuation of our previous work in heterocyclic chemistry, some of synthesized 2,6-bis(tetracarboxamide)-pyridine and macrocyclic tripeptide derivatives as analgesic, anticonvulsant and antiparkinsonian agents were screened.

MATERIALS AND METHODS

Chemistry: All the tested compounds were confirmed by physical and spectroscopic evidences according to the previously reported procedures (Khayyat and Amr, 2014).

Pharmacological screening

Experimental animals: All animals were obtained from National Research Center, Cairo, Egypt, Giza, Egypt and were acclimatized for 10 days under standard housing conditions (24±1°C; 45-55% RH with 12:12 h light/dark cycle). The animals had free access to rat food (Lipton Gold Mohr, India) and water. The animals were habituated to laboratory conditions for 48 h prior to the experimental protocol to minimize any nonspecific stress. The experimental protocol was approved by the Institutional Animal Ethics Committee by Government College of Pharmacy, Karad, India and animals were maintained under standard conditions in the animal house approved by Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Analgesic activity: "Sixty Webster mice of both sexes weighting from 20-25 g were divided into 10 groups. One group was kept as control (received saline), the second group received vehicle (Gum acacia) and the third one received+ Indomethacinas a reference drug, whereas the other groups received tested compounds (SC administration). Mice were dropped gently in a dry glass beaker of 1L capacity maintained at 55-55.5°C. Normal reaction time in seconds for all animals was determined at time intervals of 10, 20, 30, 45, 60, 90 and 120 min. This is the interval extending from the instant the mouse reaches the hot beaker till the animals licks its feet or jump out of the beaker (dose 5 mg kg^{-1}) (Tjolsen *et al*., 1991) relative potencies to Indomethacin+ were determined (Table 1).

Anticonvulsant activity: Male Webster mice (20-30 g) were individually placed in clear plastic cylinder and the tested compounds were administrated intraperitoneally (5 mg kg^{-1}), 30 min prior to a dose of 45 mg kg^{-1} of yohimbine-HCl. The animals were observed for onset and number of clonic seizures (Dunn and Fielding, 1987). Evaluation of ED_{50} values for compounds with 95% confidence limits were calculated for the antagonism of yohimbine-induced clonic seizure according to Austen and Brocklehurst (1961).

Table 1: Analgesic activities of the tested compounds (1-6) in a hot plate assay

	Analgesic activity related to indomethacin after (Mean±SE)						
Compound No.	10 min	20 min	30 min	45 min	60 min	90 min	120 min
1	1.66±0.001	1.78±0.003	1.89±0.002	1.97±0.002	2.01±0.005	2.08±0.003	2.17±0.003
2	2.34±0.003	2.48±0.002	2.58±0.002	2.87±0.00	2.90±0.004	2.98±0.001	2.91±0.003
3	2.70±0.005	3.01±0.005	3.65±0.006	4.85±0.008	4.99±0.009	5.01±0.005	5.07±0.008
4	2.57±0.001	2.61±0.004	2.79±0.003	3.21±0.006	3.87±0.002	3.90±0.002	4.10±0.006
5a	2.69±0.003	2.88±0.004	2.97±0.007	3.56±0.006	4.12±0.008	4.44±0.006	4.52±0.007
5b	3.90±0.002	4.11±0.006	4.22±0.006	5.22±0.009	6.13±0.006	6.24±0.009	6.12±0.006
5c	2.58±0.002	2.66±0.006	2.87±0.005	3.33±0.007	3.98±0.007	4.00±0.004	4.12±0.005
6a	2.80±0.004	3.21±0.006	3.87±0.008	4.99±0.009	5.16±0.008	5.22±0.007	5.27±0.006
6b	1.95±0.002	2.10±0.004	2.11±0.003	2.22±0.003	2.43±0.006	2.55±0.002	2.56±0.004
6c	2.43±0.002	2.55±0.005	2.68±0.004	2.90±0.004	3.10±0.003	3.20±0.003	3.21±0.002
Indomethacin	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Values were calculated from the mean values of data from three separate experiments and presented as mean value±SEM. All results are significant different from control values at $p \leq 0.005$. All results are significant different from reference standard values at $p \leq 0.005$

Antiparkinsonian activity (Tyahr, 1976): Groups of eight male mice (18-20 g) were used. They were dosed orally with the tested compounds (5 mg kg^{-1}) or the standard (benzatropine, 5 mg kg^{-1}) one hour prior to the administration of 0.5 mg kg^{-1} of oxotremorine s.c. Rectal temperature was measured before administration of the compounds and one hour after oxotremorine application. The score for the recorded signs are zero (absent), one (slight), two (mediums) and three (highs) (Table 1).

Acute toxicity: The oral acute toxicity of compounds was investigated using male mice (20 g each) according to previously reported methods (Verma *et al*., 1994; Litchfield and Wilcoxon, 1949). The animals were divided into groups of six mice each. The compounds were given orally, suspended in 1% gum acacia, in doses of 1, 10, 100, 200, 250 and 300 mg kg^{-1}. The mortality percentage in each group was recorded after 24 h. Additionally, the test compounds were investigated for their parenteral acute toxicity in groups of six mice each as reported earlier (Bekhit and Fahmy, 2003). The compounds, or their vehicle propylene glycol (control), were given by intraperitoneal injection in doses of 10, 25, 50, 75 and 100 mg kg^{-1}. The percentage survival was followed up to seven days".

Statistical Analysis: Results are expressed as mean±SEM Differences between vehicle control and treatment groups were tested using one-way ANOVA, followed by multiple comparisons by the Dunnett's test. A value of $p \leq 0.005$ was considered statistically significant. Dose-response curves for percent protection and ulceration were fitted by a four-parameter logistic function using a nonlinear least-squares regression.

RESULTS AND DISCUSSION

Chemistry: In continuation of our previous work, a series of peptide derivatives 1-6 (Fig. 1) were synthesized in advance and screened as antimicrobial, anti-inflammatory and anticancer agents (Khayyat and Amr, 2014). Herein, the compounds for evaluation of analgesic, anticonvulsant and antiparkinsonian activities were used.

Pharmacological activities: A series of 2,6-disubstituted pyridine ester derivatives and the corresponding amides were prepared. He pharmacological screening showed that many of these obtained compounds have good analgesic, anticonvulsant and antiparkinsonian activities comparable to voltarene®, carbamazepine® and benzotropene® as reference drugs (Amr *et al*., 2003b, 2005). On the other hand, some of new heterocyclic derivatives having a pyridine nucleus were synthesized. The 4-(5-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-pyridine and 4-(5-(2-nitrophenyl)-4H-1,2,4-triazol-3-yl) pyridine presented the best analgesic profile of this series in hot-plate, tail-flick and formalin-induced licking tests, which was partially prevented by pretreatment with mecamylamine, a nicotinic receptor antagonist (Nigade *et al*., 2012). Additionally, a simple protocol for the efficient preparation of 2-(1H-Indol-3-yl)-6-methoxy-4-arylpyridine-3,5-dicarbonitrile has been achieved through one-pot multi-component reaction under reflux condition. These compounds and bis-hantzsch dihydropyridine derivatives showed good anti-inflammatory and analgesic activities (Thirumurugan *et al*., 2010). Also, a series of novel pyridine carbohydrazide derivatives were synthesized from the reaction of 2-chloro-6-hydrazino-isonicotinic acid hydrazide with selected active reagents. All prepared compounds were tested as analgesic and anticonvulsant agents. The pharmacological screening showed that many of these compounds have good activities comparable to those of valdecoxib and carbamazepine as reference drugs (Abdel Salam *et al*., 2013).

Cell-based therapy for neuropathic pain could provide analgesics to local pain modulatory regions in a sustained, renewable fashion. In order to provide enhanced analgesic efficacy, transplantable cells may be engineered to produce complementary or increased levels of analgesic peptides (Gajavelli *et al*., 2008). Neurotensin receptors have been studied as molecular targets for the treatment of pain, schizophrenia, addiction or cancer. Neurotensin (NT) and contulakin-g, a glycopeptide isolated from a predatory cone snail *Conus geographus*, share a sequence similarity at the c-terminus, which is critical for activation of neurotensin receptors. Both peptides are potent analgesics, although affinity and agonist potency of contulakin-g toward neurotensin receptors are significantly lower, as compared to those for NT (Lee *et al*., 2015). The influence of Delta-Sleep Inducing Peptide (DSIP) upon seizures induced by corazol, bicuculline, picrotoxin, strychnine, thiosemicarbazide were investigated in experiments on F1 (CBA×C57 BL/6) mice. It was shown that DSIP increased the latency of first seizure manifestation, which were induced by corazol, bicuculline and picrotoxin and also resulted in a suppression of seizure severity of corazol and bicuculline induced seizures.

Anticonvulsant action of DSIP was evident under the condition of the mild severity seizures development. The effect of DSIP was mostly pronounced in range of its doses from 10-100 μg kg^{-1}. The DSIP when combined with

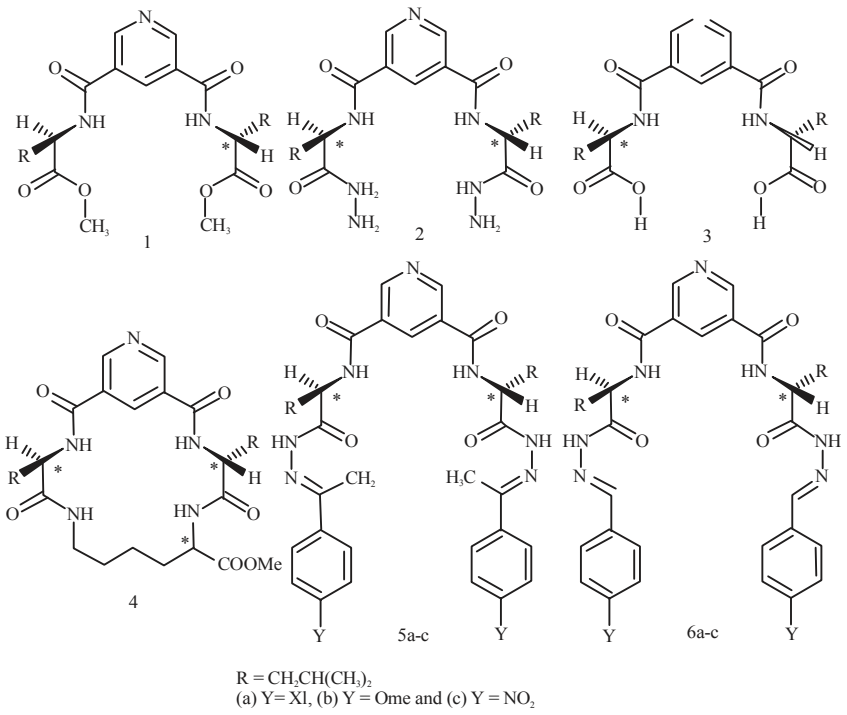

Fig. 1: Chemical structure for the tested compounds 1-6 (Khayyat and Amr, 2014)

phenobarbital, carbamazepine, diphenylhydantoin or nicotinamide enhanced the antiepileptic effects of these anticonvulsant drugs (Shandra *et al*., 1989). A series of dipeptide derivatives of L-dopa were synthesized and investigated for their pharmacological activity using the unilaterally 6-hydroxydopamine (6-OHDA)-lesioned rat as an experimental model of Parkinson's disease. Among them, (S)-isopropyl 2-(2-amino-2-methylpropanamido)-3-(3,4-dihydroxy phenyl) propanoate (4 g) was found to be the most active compound, with 106% AUC activity and 149% peak activity of L-dopa after oral administration (Zhou *et al*., 2013). In view of all aforementioned data that confirmed that many biological active peptides tat have analgesic anticonvulsant and antiparkinsonian activities, the tested compounds were screened for their have analgesic anticonvulsant and antiparkinsonian activities.

Analgesic activities: All compounds tested exhibited analgesic activities in a hot plate assay (Table 1). Compound 5b was the most potent one that have 3-6 folds the activity of indomethacin through 10-120 min with longer duration of activity. Compounds 6a, 3, 5a, 5c, 4, 6c and 2, where less potent than compound 5b and they were arranged in according to their analgesic potencies. Also, they are exhibited both high onset of analgesic activities and longer duration of analgesic activities that lasted for more than 2 h. Compounds 6b and 1 were the least potent analgesic activities with sustained duration of action.

Interesting enough all tested compounds having analgesic activities higher than that of indomethacin.

Anticonvulsant activities: Compounds with anticonvulsant activity provide no protection against yohinobine-induced clonic seizures. Compounds 5b, 6a and 3 showed the most potent interesting anticonvulsant activities with ED_{50} 78.87, 84.87 and 88.90 μM kg^{-1}, respectively. Compounds 5a, 5c, 4, 6c and 2 showed moderate anticonvulsant activities with ED_{50} 93.29, 98.11, 103.29, 108.14 and 110 μM kg^{-1}, respectively. Compounds 6b and 1 showed the least anticonvulsant activities with ED_{50} 123.20 and 127.17 μM kg^{-1}, respectively. All tested compounds were more active than carbamazepine (Table 2).

Antiparkinsonian activities: "The muscarinic agonists Tremorine® and Oxotremorine® induce parkinsonian signs, such as tremor, ataxia, spasticity, salivation, lacrimation and hypothermia. Antiparkinsonian agents antagonize these signs. The antiparkinsonian activity measured by the ability of compounds to protect animals against the parkinsonian like signs induced by agonists. Compounds 5b and 6a, showed the most potent antiparkinsonian activities (relative potencies to benzatropine® (=1.0) were 2.24 and 2.08, respectively.

Table 2: Anticonvulsant activities of the tested compounds (1-6) (as ED_{50} values) needed to antagonize yohimbine-induced clonic seizure

Compound No.	ED_{50} (μM kg^{-1})
Carbamazepine	160.30±1.12
1	127.17±0.98
2	110.23±0.98
3	88.90±0.75
4	103.29±0.86
5a	93.29±0.73
5b	78.87±0.43
5c	98.11±0.87
6a	84.87±0.54
6b	123.20±0.99
6c	108.14±0.83

Values were calculated from the mean values of data from three aspartate experiments and presented as mean value±SEM. All results are significant different from control values at $p \leq 0.005$. All results are significant different from reference standard values at $p \leq 0.005$

Table 3: Antiparkinsonian activities of the tested compounds (1-6) compared to that of benzatropine

Compound No.	Salivation and lacrimation score	Tremors score	Oxotremorine rectal temperature (%)±SE	Relative potency to Benzatropine mesilatered to±SE
Control	0	0	0	0
Benzatropine	1	1	25±0.86	1.00± 0.09
1	1	1	32±0.55	1.28±0.02
2	1	1	35±0.47	1.40±0.01
3	1	1	48±0.73	1.92±0.02
4	1	1	39±0.38	1.56±0.02
5a	1	1	45±0.42	1.80±0.01
5b	1	1	56±0.75	2.24±0.02
5c	1	1	41±0.27	1.64±0.02
6a	1	1	52±0.64	2.08±0.01
6b	1	1	34±0.66	1.36±0.03
6c	1	1	37±0.79	1.48±0.03

Values were calculated from the mean values of data from three separate experiments and presented as mean value±SEM. All results are significant different from control values at $p \leq 0.005$. All results are significant different from reference standard values at $p \leq 0.005$

Table 4: Acute toxicity of the tested compounds (1-6)

Compound No.	LD_{50} (mg kg^{-1})
1	2577.67±6.02
2	2789.95±5.03
3	3656.39±4.94
4	3908.86±6.82
5a	2767.77±5.75
5b	2334.50±4.36
5c	3889.98±6.47
6a	2545.60±7.58
6b	2468.88±9.69
6c	2890.04±8.49

Values were calculated from the mean values of data from three separate experiments and presented as mean value±SEM. All results are significant different from control values at $p \leq 0.005$

Compounds 3 and 5a showed moderate antiparkinsonian activities (relative potencies to benzatropine® (=1.0) were 1.92 and1.8, respectively. While compounds 5c, 4, 6c, 2, 6b and 1, showed the least antiparkinsonian activities (relative potencies to Benzatropine® (=1.0) were, 1.64, 1.56, 1.48 and 1.40, 1.36 and 1.28). All tested compounds are more potent than the Benzatropine (Table 3).

Acute toxicity: Compounds 3, 4 and 5c showed high LD_{50} mainly above 3 g kg^{-1}, while other compounds showed moderate LD_{50} mainly above 2 g kg^{-1}.This profile confirmed high marginal profile of safety (Table 4).

CONCLUSION

All tested compounds showed analgesic, antipakinsonian and anticonvulsant activities and the order for these activities were 5b, 6a, 3, 5a, 5c, 4, 6c, 2, 6b and 1.

Structure activity relationship: Careful examination of the relation between chemical structure and a pharmacological activities culminated on the following assumptions:

- Macromolecules with larger peptide units essential for higher activities
- Closed macrolide structures provide moderate activities
- Chlorine atom provides higher activities than nitro group
- Generally derivatives 5 more active than derivatives 6 due to the presence of methyl group that ascensional for removate cage deformations that contributes to receptor binding activities

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