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RESEARCH ARTICLE

Synthesis, *in silico* metabolic and toxicity prediction of some novel imidazolinones derivatives as potent anticonvulsant agents

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Abstract

A series of 1,2,4-trisubstituted 5-imidazolinone derivatives were synthesized by Erlenmeyer condensation of benzoylglycine (hippuric acid) with different aldehydes in the presence of sodium acetate and acetic anhydride. The derivatives of the compounds were prepared by condensation of some known sulpha drugs with 5-oxazolone derivatives. The anticonvulsant activity of the compounds was determined by the protection of pentylenetetrazole-induced convulsions that was ranged from 10 to 60%. The compounds with *p*-OCH_3, *p*-OH and *o*-Cl substitutions in the phenyl ring on 4th position of the imidazolinone ring exhibited good anticonvulsant activity. *In silico* metabolic and toxicity studies showed that all the compounds in the series are not likely to exhibit toxicity except the compounds IIIa, IIIb, VIa and VIb, that is predicted to show 29% mutagenicity and 53% irritation in comparison to the other compounds. The predicted lethal effect and hERG toxicity of the compounds showed that IIa, IVa, Va and Vb might be toxic at higher concentrations. The results successfully establish the synthesized imidazolinone derivatives as novel compounds with anticonvulsant properties, low predicted cardiotoxicity and lethal effects thus can be promising leads for further development as novel anticonvulsants.

Keywords: Imidazolinone, *in silico*, anticonvulsant, toxicity, hERG

Introduction

The development of a new bioactive molecule is complex, time consuming and very expensive and also the developed drugs may suffer from unwanted side effects, toxicity, resistance, etc. It is the primary thought of the scientist in the medicinal chemistry field to develop safe and potent molecules. The last two decades is called in neuroscience as "decade of the brain" and it has brought advances to the treatment of neurological disabilities, including epilepsy[1]. Epilepsy, a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia manifesting as brief episodes (seizures) of loss of or disturbances of consciousness[2,3]. Although several classes of anti-epileptic agents with different nucleus are available for treating epilepsy, these agents have a number of shortcomings which limit their utility[4–6].

Imidazolinone is an important scaffold possessing a spectrum of pharmacological actions, which includes anticonvulsant, antiparkinsonism and monoamino-oxidase inhibitory activities[7–12]. A careful scrutiny of structure activity relationship studies of anticonvulsant agents reported in literature indicates that ureido moiety is responsible for the anticonvulsant action[13–15]. Precedence exist in literature on anticonvulsant properties of 1,2,4-trisubstituted 5-imidazolinones[12], the N arylation of imide NH of the imidazolinone could serve two functions; increases the partition coefficient and prevents the dissociation of imido hydrogen, three both cases favored more effective distribution of the central nervous system[16]. The multiple biological properties of sulfonamides are well documented in literature[17,18]. The present study aims to introduce two sulfa drugs sulfamethoxazole and

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sulfadoxin into 4-arylidene-2-phenyl-5-(4H)-oxazolones to formulate 1,2,4-trisubstituted 5-imidazolinones bearing sulfonamide moiety with the hope that combination of these active groups in the new molecular design would lead to better anticonvulsant agents. Based on the aforementioned, we have designed and synthesized trisubsituted imidazolinone compounds incorporating sulfa drugs (sulfamethoxazole and sulfadoxin) and evaluated them *in vivo* for ascertaining their anticonvulsant efficacy.

ADME-Tox property of molecules is an important parameter for the success of some compounds in clinic. *In silico* methods to predict toxicity and ADME properties even before a drug candidate was synthesized is widely used in drug discovery to understand the properties that are necessary to convert leads into good medicines, which increase the success rate[19,20]. Drug metabolism and clearance determine the success of a drug, as these properties have a significant impact on bioavailability (oral or intravenous) and give an idea about how a drug behave in the human body. The recognition of the metabolic site could be of great help in designing new compounds with better pharmacokinetic profile as well as to avoid the presence of toxic metabolites by chemically protecting the metabolic labile moieties in the drug candidate[21–24]. Related to the foregoing, the synthesized compounds were subjected to *in silico* toxicity and metabolism studies in order to predict their metabolic and toxicity profile. A preliminary idea of the metabolic and toxicity profile of a compound could be of great help in assessing the suitability of the proposed molecule as a probable anticonvulsant drug candidate and as well as to avoid the presence functionalities that might lead to toxic metabolites.

Materials and methods

Materials used

Melting points were determined on electrothermal capillary melting point apparatus and were uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel G on glass plate as stationary phase and benzene: ethylacetate (80:20) as mobile phase. IR (KBr) (cm^{-1}) spectra were recorded on FT/IR-470 Plus Jasco spectrophotometer. ^1H NMR spectra were recorded on Brucker DRx (300 MHz) spectrometers and the chemical shift values are reported in parts per million using tetramethylsilane as internal standard. The samples were dissolved in $CDCl_3$.

Synthesis of 4-arylidene-2-phenyloxazol-5(4H)-one derivatives

A mixture of 0.025 mol of redistilled benzaldehyde derivatives, 4.48 g (0.025 mol) of benzoyl glycine (hippuric acid), 7.66 g (0.075 mol) of acetic anhydride and 2.05 g (0.025 mol) of anhydrous sodium acetates were placed in a 100 ml were placed in a conical flask and heated on an electric hotplate with constant stirring till liquified. As soon as the mixture had liquefied completely, the flask was transferred on to a water bath and heated at 60°C for 2 h. Then 100 ml of ethanol was added slowly to the content of the flask and allowed the mixture to stand overnight. The crystalline product was filtered with suction and washed with two 25 ml portion of ice cold alcohol and then washed with two 25 ml portion of boiling water and dried at 100°C. The yield of almost pure oxazolone, m.p. 165–166°C was 4 g (64%). Recrystallization from benzene raises the m.p. to 167–168°C.

Synthesis of 1-N-substituted 4-(4-benzylidene-5-oxo-2-phenyl-4,5dihydro-1H-imidazol-1-yl) benzenesulfonamide

4-Arylidene-2-phenyloxazol-5(4H)-one derivatives (0.004 mol) was heated with an equimolar quantity of sulfonamide (sulfamethoxazole and sulfadoxin) in an oil bath at 140°C for 1 h. The resulting jelly like mass was taken in an organic solvent (acetone) and refluxed for 8 h with continuous removal of water and cooled, the excess solvent removed under vacuum and the resultant solid was collected. Crude solid product was recrystallized from ethyl acetate to get flakes of 5-imidazolinones and found chromatographically homogenous when detected with iodine.

Determination of anticonvulsant activity

Anticonvulsant activity was determined against pentylenetetrazole-induced seizures in mice, 25–30 g of either sex[11,12,14]. The mice were divided into groups of five mice and keeping the group weight as near as possible. All compounds were suspended in 5% aqueous gum acacia (have devoid of anticonvulsant activity) to give a concentration of (0.025% w/v). An arbitary dose of 100 mg/kg i.p. of imidazolinone was administered to five mice. The mice were then injected with pentylenetetrazole (90 mg/kg i.p.) 30 min after the administration of the test compounds. The pentylenetetrazole has been shown to produce convulsions in almost all untreated mice and to exhibit 100% mortality during 24 h. No mortality of animals was observed during 24 h treatment with 100 mg/kg of the imidazolinones alone. The mice were observed 60 min for the occurrence of seizures and an episode of clonic spasm persisting for a minimum of 5 s was considered a threshold convulsion. Transient intermittent jerks and tremulousness were not counted. Mice devoid of threshold convulsions during 60 min were considered protected. The number of mice protected in each group was recorded and the anticonvulsant activity of these imidazolinone was represented as percent protection.

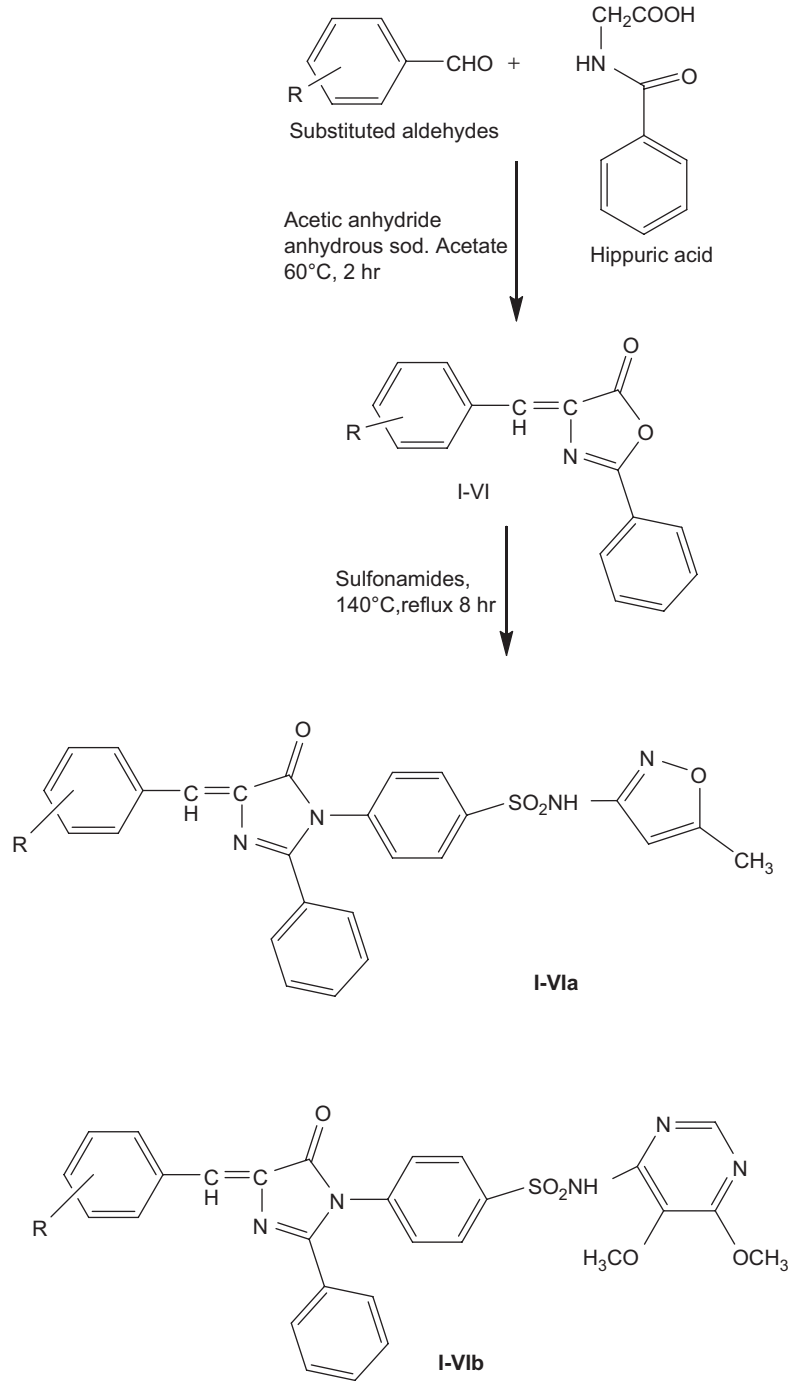
In silico metabolites and toxicity prediction

The metabolites and the toxicity profile of the compounds were predicted by computational method using Pallas 3.1.1.2. ADME-Tox prediction software[25]. The LD_{50} and the hERG (pIC_{50}) were predicted using q-Tox and q-hERG softwares, respectively[26].

Results and discussion

Chemistry

The oxazolone derivatives were synthesized by the condensation of benzaldehyde and hippuric acid in acetic anhydride and anhydrous sodium acetate. 1,2,4-trisubstituted 5-imidazolinones derivatives were synthesized by the condensation of some known sulpha drugs (sulfamethoxazole and sulfadoxin) with 5-oxazolone derivatives. The imidazolinone derivatives were synthesized employing a two step procedure as outlined in scheme 1. The physicochemical characterization was performed in order to confirm the progress of reaction and the purity of compounds. TLC was carried out on silica gel G using benzene: ethyl



Structures: I = H, II = *p*-dimethylamino, III = *p*-OH, IV = *p*-OCH_3, V = *o*-Cl, VI = *o*-OH

Scheme 1. Synthesis of proposed imidazolinone derivatives.

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acetate (80:20) as eluent (Table 1). The constitutions of the synthesized compounds were confirmed by IR and NMR. The functional groups on the compounds were confirmed by IR spectroscopy and the number and the environment of hydrogen atoms in the compounds were confirmed by NMR spectrum (Table 2). The anticonvulsant activity of the compounds (as per ethical guidelines) was determined by ascertaining the percentage protection against pentylenetetrazole-induced convulsions in mice and the activity of the synthesized compounds ranged from 10 to 60%. Amongst the compounds tested, maximal protection was observed for compounds with *p*-OCH_3 (IVa), *p*-OH (IIIa) substitution in phenyl ring on the 4th positions of the imidazolinone ring of series bearing sulfamethoxazole moiety, and *p*-OCH_3 (IVb), *o*-Cl (Vb), substitutions in the phenyl ring on the 4th positions of the imidazolinone ring of series bearing sulfadoxin moiety. In case of the unsubstituted compounds, the compound Ib with sulfadoxin moiety showed better protection (20%) compared to the compound Ia with sulfamethoxazole moiety suggesting that incorporation of sulfadoxin in the nucleus is most favoured for anticonvulsant activity exhibited by the title compounds. In sulfamethoxazole series, p-dimethyl amino substitution (IIa) and *o*-OH substitution (VIa) in the phenyl ring resulted in two fold increase in the protection whereas *o*-Cl substitution (Va) caused a fourfold increase in protection against pentylenetetrazole-induced convulsions in comparison to the unsubstituted compound Ia.

Table 1. Anticonvulsant activity of the synthesized compound.

Compound No	Mol. Formula	Mol. Wt	M.P. (°C)	% Yield	Anticonvulsant activity % protection
Ia	$C_{26}H_{20}N_4O_4S$	484.55	126	61	10
Ib	$C_{28}H_{23}N_5O_5S$	541.60	160	47	20
IIa	$C_{28}H_{25}N_5O_4S$	527.16	170	60	20
IIb	$C_{30}H_{28}N_6O_5S$	584.67	166	74	20
IIIa	$C_{26}H_{20}N_4O_5S$	500.12	134	93	60
IIIb	$C_{28}H_{23}N_5O_6S$	557.58	130	95	40
IVa	$C_{27}H_{22}N_4O_5S$	514.57	80	89	60
IVb	$C_{29}H_{25}N_5O_6S$	571.62	84	87	60
Va	$C_{26}H_{19}ClN_4O_4S$	518.97	80	65	40
Vb	$C_{28}H_{22}ClN_5O_5S$	576.02	85	53	60
Via	$C_{26}H_{20}N_4O_5S$	500.55	108	84	20
VIb	$C_{28}H_{23}N_5O_6S$	557.56	164	83	40
Reference	Phenobarbital				100

Table 2. Analytical spectra data of the synthesized compounds.

Compound No	Spectra details
Ia	IR (KBr) (cm^{-1}) 3194 (Ar-CH), 1723 (C=O), 1641 (C=N), 1169 (S=O); ^1H NMR ($CDCl_3$) 2.29 (s, 3H, CH_3), 4.00 (s, 1H, SO_2NH), 6.20 (s, 1H, -CH oxazole), 7.36 (s, 1H, C=CH), 7.10–8.90 (m, 14H, Ar-H).
Ib	IR (KBr) (cm^{-1}) 3102 (Ar-CH), 1731 (C=O), 1651 (C=N), 1162 (S=O); ^1H NMR ($CDCl_3$) 3.81–3.90 (bs, 6H, OCH_3), 4.70 (s, 1H, SO_2NH), 7.56 (s, 1H, C=CH), 7.10–8.80 (m, 14H, Ar-H), 9.20 (s, 1H, -CH pyrimidine).
IIa	IR (KBr) (cm^{-1}) 3161 (Ar-CH), 1716 (C=O), 1646 (C=N), 1161 (S=O), 1374 (C-N); ^1H NMR ($CDCl_3$) 2.42 (s, 3H, CH_3), 2.90 (s, 6H, $N(CH_3)_2$), 4.10 (s, 1H, SO_2NH), 6.23 (s, 1H, -CH oxazole), 6.55 (s, 1H, C=CH), 6.50–7.80 (m, 13H, Ar-H).
IIb	IR (KBr) (cm^{-1}) 3239 (Ar-CH), 1716 (C=O), 1647 (C=N), 1321 (S=O); ^1H NMR ($CDCl_3$) 3.28–3.40 (bs, 6H, OCH_3), 2.87 (s, 6H, $N(CH_3)_2$), 4.10 (s, 1H, SO_2NH), 6.60 (s, 1H, C=CH), 7.20–8.20 (m, 13H, Ar-H), 9.11 (s, 1H, -CH pyrimidine).
IIIa	IR (KBr) (cm^{-1}) 3379 (OH), 3098 (Ar-CH, 1758 (C=O), 1653 (C=N), 1324 (S=O); ^1H NMR ($CDCl_3$) 2.25 (s, 3H, CH_3), 4.00 (s, 1H, SO_2NH), 6.00 (s, 1H, OH), 6.30 (s, 1H, -CH oxazole), 7.60 (s, 1H, C=CH), 6.68–7.90 (m, 13H, Ar-H).
IIIb	IR (KBr) (cm^{-1}) 3473 (OH), 3248 (Ar-CH), 1733 (C=O), 1654 (C=N), 1351 (S=O); ^1H NMR ($CDCl_3$) 3.8–4.0 (bs, 6H, OCH_3), 4.21 (s, 1H, SO_2NH), 6.10 (s, 1H, OH), 7.60 (s, 1H, C=CH), 6.78–7.90 (m, 13H, Ar-H), 9.20 (s, 1H, -CH pyrimidine).
Iva	IR (KBr) (cm^{-1}) 3063 (Ar-CH), 1732 (C=O), 1636 (C=N), 1325 (S=O); ^1H NMR ($CDCl_3$) 2.39 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 4.00 (s, 1H, SO_2NH), 6.52 (s, 1H, -CH oxazole), 7.51 (s, 1H, C=CH), 6.21–7.90 (m, 13H, Ar-H).
IVb	IR (KBr) (cm^{-1}) 3102 (Ar-CH), 1716 (C=O), 1653 (C=N), 1311 (S=O) 1210 (C-O-C); ^1H NMR ($CDCl_3$) 3.71–3.90 (ts, 9H, OCH_3), 4.00 (s, 1H, SO_2NH), 7.59 (s, 1H, C=CH), 6.71–7.90 (m, 13H, Ar-H), 9.40 (s, 1H, -CH pyrimidine).
Va	IR (KBr) (cm^{-1}) 3289 (Ar-CH), 1731 (C=O), 1616 (C=N), 1338 (S=O) 1165 (C-O); ^1H NMR ($CDCl_3$) 2.32 (s, 3H, CH_3), 4.00 (s, 1H, SO_2NH), 6.72 (s, 1H, -CH oxazole), 7.79 (s, 1H, C=CH), 7.00–7.90 (m, 13H, Ar-H).
Vb	IR (KBr) (cm^{-1}) 3239 (Ar-CH), 1734 (C=O), 1651 (C=N), 1318 (S=O); ^1H NMR ($CDCl_3$) 3.81 (s, 6H, OCH_3), 4.22 (s, 1H, SO_2NH), 7.76 (s, 1H, C=CH), 7.00–7.90 (m, 13H, Ar-H), 9.40 (s, 1H, -CH pyrimidine).
Via	IR (KBr) (cm^{-1}) 3235 (Ar-CH), 1764 (C=O), 1666 (C=N), 1326 (S=O); ^1H NMR ($CDCl_3$) 2.34 (s, 3H, CH_3), 4.10 (s, 1H, SO_2NH), 5.20 (s, 1H, OH), 6.40 (s, 1H, -CH oxazole), 7.80 (s, 1H, C=CH), 6.68–7.90 (m, 13H, Ar-H).
Vib	IR (KBr) (cm^{-1}) 3376 (OH), 3241 (Ar-CH), 1765 (C=O), 1650 (C=N), 1320 (S=O); ^1H NMR ($CDCl_3$) 3.80 (s, 6H, OCH_3), 4.00 (s, 1H, SO_2NH), 4.80 (s, 1H, OH), 7.80 (s, 1H, C=CH), 6.68–7.90 (m, 13H, Ar-H), 9.20 (s, 1H, -CH pyrimidine).

In sulfadoxin series, *p*-dimethyl amino substitution (IIb) in phenyl ring did not improve the anticonvulsant activity whereas, *p*-OH (IIIb) and *o*-OH (VIb) substitution in phenyl ring improved anticonvulsant activity two-fold in comparison to the unsubstituted compound Ib. It is worth mentioning that the majority of the compounds have shown significant activity.

In silico metabolites and toxicity of the synthesized compounds were predicted by using Pallas 3.1.1.2., q-Tox and q-hERG software and the result obtained are tabulated in Table 3. The possible position of metabolism of the synthesized compounds is given in Figures 1 and 2. All the compounds appear to undergo hydroxylation at the *para* and *meta* position of the phenyl ring. N-oxidation of the aromatic heterocycles in the oxazole and pyrimidine ring occurred alongwith oxidation of the tertiary nitrogen atom in the imidazolinone ring. The imidazolinone ring has cleaved in all compounds. The methoxy compounds especially pyrimidine substituents containing compounds (Ib to VIb) and *p*-methoxy phenyl substituents (IVa) of the compounds undergo demethylation to give a free phenolic group. The results show that all the compounds in the series are expected to undergo phase I metabolism such as oxidation, hydration, ring cleavage, etc. (Figures 1 and 2). Only hydroxyl group containing compound IIIa,b and VIa,b are expected to undergo phase II metabolism of O-glucouronide conjugation and phenol sulfate conjugation.

The compounds except IIIa,b and VIa,b shows toxicity. All the compounds in this series show 0% toxicity in terms of oncogenicity and sensitivity. The teratogenic properties of the compounds are <50% which shows the probability of this toxicity is less. The compounds IIIa,b and VIa,b have >50% (53%) overall toxicity compared to other compounds (34%) and these four compounds exhibit irritation 53% and mutragenicity 29%. It shows that these compounds are more toxic than all other compounds. These compounds only give phase II metabolites due to the presence of OH group in the benzene ring as phenolic OH.

The predicted LD_{50} and the pIC_{50} (hERG toxicity) of the compounds show that the compounds IIa, IVa, Va and Vb might have lethal effect at high concentration and may also possess the cardiotoxicity in high concentration compared with other compounds. These compounds also exhibit significant anticonvulsant activities than other compounds. In comparison with the other toxicity studies as mentioned earlier, the compound with –OH groups in phenyl rings of their structure are more toxic

Table 3. Predicted toxicities of the synthesized compounds.

Compound No	hERG (pIC_{50})	LD_{50} (pIC_{50})	Mutagenicity	Teratogenicity	Irritation
Ia	7.5	0.8	0	34	0
Ib	5.6	–0.2	0	34	0
IIa	6.5	0.7	0	34	0
IIb	7.4	0.2	0	34	0
IIIa	7.7	1.4	29	34	53
IIIb	7.2	–0.5	29	34	53
Iva	6.5	0.4	0	34	0
IVb	7.3	1.0	0	34	0
Va	6.8	0.8	0	34	0
Vb	6.3	1.1	0	34	0
VIa	7.3	1.5	29	34	53
VIb	7	0.7	29	34	53

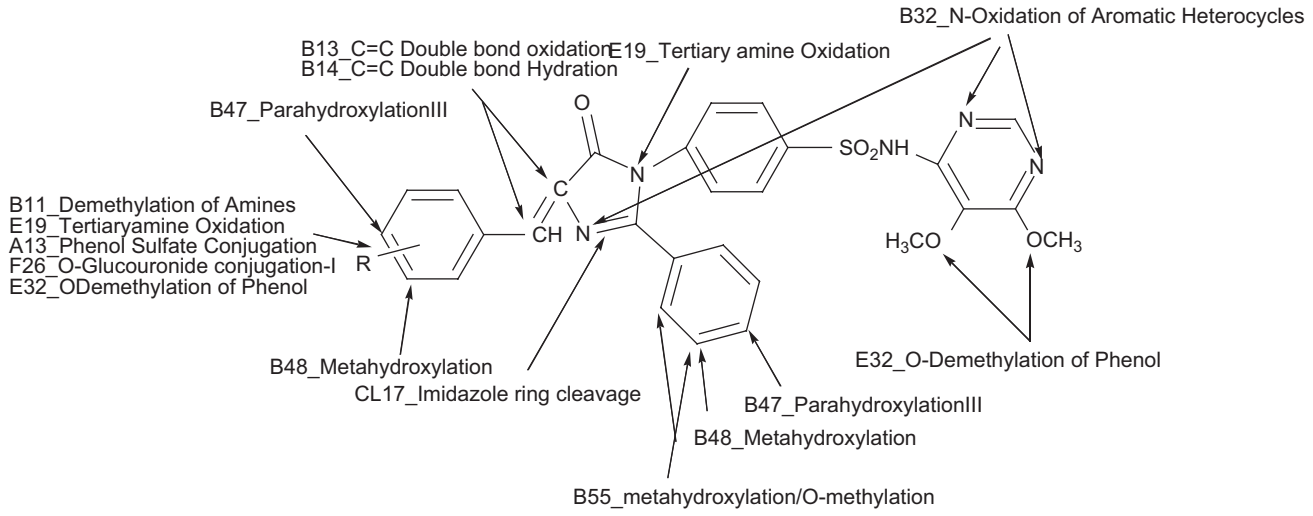

Figure 1. Predicted metabolic position of imidazolinones (Ia–VIa) derivatives.

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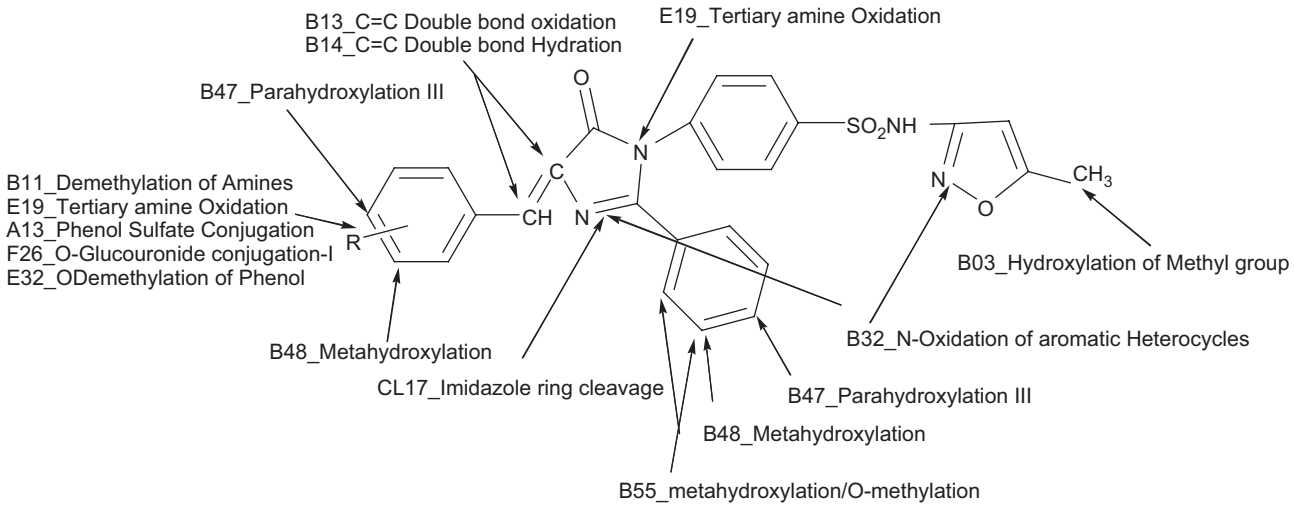

Figure 2. Predicted metabolic position of imidazolinones (Ib–VIb) derivatives.

than others. Unfortunately the –OH substitution at the *para* position on the phenyl ring of the molecule has considerably significant anticonvulsant activity.

Summarizing the above, it can be concluded that we have successfully synthesized 12 newly designed derivatives of 1,2,4-trisubstituted 5-imidazolinones incorporating two sulfa drugs. All the title compounds have been investigated for their anticonvulsant activity in mice models. Interestingly, the majority of the compounds showed moderate to very good anticonvulsant activity. The best results in terms of the percentage protection against pentylenetetrazole-induced convulsions in mice was achieved for compounds with *p*-OCH_3 and *p*-OH substitution in the phenyl ring on the 4th positions of the imidazolinone ring for sulfamethoxazole series and *p*-OCH_3 and *o*-Cl substitution in the phenyl ring on the 4th positions of the imidazolinone ring for sulfadoxin series. *In silico* metabolite and toxicity studies were also performed for the synthesized molecules to assess their suitability in terms of their susceptibility to metabolism and toxicity profile. Overall, the studies establish 1,2,4-trisubstituted 5-imidazolinones as novel leads for further exploration as anticonvulsant agents.

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Declaration of interest

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