Synthesis of γ-butyrolactone hybrid imidazo[2,1-b][1,3]-thiazoles from limonene

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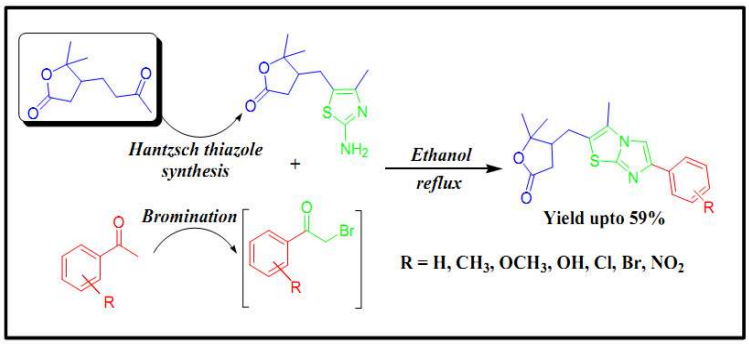
Abstract. The substituted γ-butyrolactones are important structural motifs in several natural products and pharmaceuticals. In this paper γ-butyrolactone fused heterocyclic imidazo[2,1-b][1,3]-thiazole derivatives have been synthesized from thiazole amine (**4**) and different substituted α-bromo acetophenones in moderate yields. Electron rich substituents provided higher yields of the desired products. The screening results of physicochemical properties indicated that all the synthesized heterocyclic molecules could be good drug candidates.



Keywords: γ-butyrolactone; thiazole; imidazothiazole; α-bromo acetophenones

1. Introduction

Levamisole (a, Figure 1) is a broad spectrum anthelminthic, belongs to a class of synthetic imidazo[2,1-b][1,3]-thiazole derivatives.[1] This heterocyclic skeleton is very important class in medicinal chemistry because of their several therapeutic properties.[2] These derivatives have been used as anti-hypertensive, anti-inflammatorie, immunosuppressive, fungicide, herbicide, antitumor[3], and cardiotonic agent.[4,5] Few reports are available on the synthesis of substituted imidazo[2,1-b][1,3]-thiazole derivatives such as, guanylhydrazone derivatives[6], sulfides and sulfone derivatives.[7] Bakherad *et al.*[8] have prepared imidazothiazoles using polystyrene supported palladium complex during sonogashira coupling.

The functionalized γ-butyrolactones are the building blocks in the synthesis of a number of natural products and biologically relevant compounds[9], for example, precursors of inhibitors of HIV-1 protease, alkaloids, macrocyclic antibiotics, lignans, pheromones, antileukemics and flavor component[10-13]. Due to various pharmacological and medicinal properties, the synthesis of its analogues constitutes an active area in organic synthesis[14-17].

From last few years, we have been engaged in the development of chemistry and biological activities of different amines, thiazole, thiazole amide, sulphonamides and α,β-unsaturated carbonyl compounds from naturally abundant molecules like limonene, himachalenes etc. In our previous report[18-21], we have described the regioselective

bromination, followed by nucleophillic substitution with amines and thiourea for the formation of γ-butyrolactone substituted amines and thiazole derivatives. Gamma butyrolactones fused with heterocyclic systems could be interesting entries for biological activities. Therefore, we were interested in synthesizing nitrogen and sulfur containing heterocycles hybrid with γ-butyrolactones. To the best of our knowledge, imidazo[2,1-b][1,3]thiazole fused γ-butyrolactone moiety has not yet been reported by any group. Hence, in the continuation to our previous work, herein we have attempted to synthesize γ-butyrolactone hybrid imidazo[2,1-b][1,3]thiazole derivatives (b, Figure 1) with different electron withdrawing and donating groups substituted at phenyl ring.

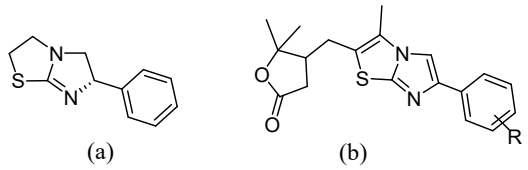


Figure 1 Structures of (a) Levamisole 1 (b) synthesized γ-butyrolactone fused imidazo[2,1-b][1,3]-thiazole derivatives.

2. Experimental

2.1 General

Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Column chromatography was carried out using silica gel (60-120 mesh). TLC was performed on aluminum plates coated with Silica gel 60 with F_{254} indicator. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a 300 MHz. ^{1}H NMR and ^{13}C NMR chemical shifts are expressed in parts per million (δ). High resolution mass spectra (HRMS) were obtained under positive electron spray ionization (*m/z* values are given). Optical rotations were measured in Horiba Sepa-300 Polarimeter.

2.2 Synthesis of compounds

*2.2a 5,5-Dimethyl-4-(3-methyl-6-phenyl-imidazo[2,1-b]thiazol-2-ylmethyl)-dihydro-furan-2-one (**5a**):* A solution of acetophenone (0.83 mmol) in diethyl ether (1 ml) was placed in a round bottomed flask. The solution was cooled in ice bath and catalytic amount of anhydrous $AlCl_3$ was introduced and Br_2 solution (0.83 mmol) was added drop wise with stirring. After few minutes the bromine color disappeared with the evolution of HBr. After the completion of reaction, ether and HBr were removed under vacuum on rotary evaporator and **3a** was formed. This compound **3a** was dissolved in dry ethanol (2 ml) and thiazole amine **4** (0.83 mmol) was added to it and refluxed for about 24 hrs. After the completion of reaction, ethanol was evaporated on rotary evaporator and reaction mixture was dissolved in dichloromethane and washed with minimum amount of $NaHCO_3$ solution and then with water. It was dried over anhydrous sodium sulphate and concentrated in a rotary evaporator. Purification was performed by silica gel column chromatography using hexane:ethyl acetate (50:50 to 100:0) to give **5a** as white ppts. (0.167 g, 59%). m. pt 210-212 °C; $[\alpha]_D^{27}$ -90° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82-7.85 (*m*, 2H), 7.55-7.62 (*m*, 1H), 7.39-7.44 (*m*, 2H), 7.30-7.32 (*m*, 1H), 2.80-3.00 (*m*, 1H), 2.68-2.76 (*m*, 2H), 2.38-2.58 (*m*, 1H), 2.40 (*s*, 3H), 1.53-1.70 (*m*, 1H), 1.42 (*s*, 3H), 1.27 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9 (C), 147.2 (C), 147.1 (C), 134.2 (C), 129.0 (2CH), 127.8 (CH), 125.5 (2CH), 124.1 (C), 121.4 (C), 106.7 (CH), 86.3 (C), 46.8 (CH), 35.1 (CH), 30.0 (CH_2), 28.0 (CH_3), 22.5 (CH_3), 11.8 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{19}H_{21}N_2O_2S$ 341.4472, obsd. 341.4478

2.2b 5,5-Dimethyl-4-(3-methyl-6-p-tolyl-imidazo[2,1-b]thiazol-2-ylmethyl)-dihydro-furan-2-one ***(5b):*** White ppts. (0.145 g, 55 %); m. pt 218-220 °C; $[\alpha]_D^{27}$ -105° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.7 (*d*, 2H, *J*=7.5 Hz), 7.5 (*s*, 1H), 7.2(*d*, 2H, *J*=7.9 Hz), (2.88-2.83 (*m*, 1H), 2.72-2.64 (*m*, 2H), 2.55-2.53 (*m*, 1H), 2.38 (*s*, 3H), 2.36 (*s*, 3H), 2.20-2.18 (*m*, 1H), 1.50 (*s*, 3H), 1.39 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (C), 147.2 (2C), 137.2 (C), 131.4, (C), 129.5 (2CH), 125.1 (2CH), 123.8 (C), 120.9 (C), 105.9 (CH), 85.9 (C), 46.6 (CH), 34.9 (CH_2), 27.8 (CH_2), 27.8 (CH_3), 22.3 (CH_3), 21.3 (CH_3), 11.6 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{20}H_{23}N_2O_2S$ 355.4738, obsd. 355.4730.

2.2c 4-[6-(4-Methoxy-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-ylmethyl]-5,5-dimethyl-dihydro-furan-2-one ***(5c):*** White ppts (0.140 g, 57 %); m. pt. 205-207 °C; $[\alpha]_D^{27}$ -98° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.71 (*d*, 2H, *J*=9.0 Hz), 7.43 (*s*, 1H), 6.94-6.91 (*d*, 2H, *J*=9.0 Hz), 3.82 (*s*, 3H), 2.81-2.79 (*m*, 1H), 2.69-2.63 (*m*, 2H), 2.40-2.60 (*m*, 1H), 2.38-2.35 (*m*, 1H), 2.33 (*s*, 3H), 1.48 (*s*, 3H), 1.36 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (C), 159.5 (C), 147.2 (C), 147.1 (C), 127.2 (C), 126.7 (2 CH), 124.1 (C), 120.9 (C), 114.5 (2 CH), 105.6 (CH), 86.1 (C), 55.6 (CH_3), 46.8 (CH), 35.1 (CH_2), 27.9 (CH_2), 27.9 (CH_3), 22.5 (CH_3), 11.8 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{20}H_{23}N_2O_3S$ 371.4732, obsd. 371.4739

2.2d 4-[6-(3-Methoxy-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-ylmethyl]-5,5-dimethyl-dihydro-furan-2-one ***(5d):*** Off white ppts. (0.130g, 53 %);m. pt. 218-220 °C; $[\alpha]_D^{27}$ -110° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, *pyridine* d_5): δ 8.20 (*s*, 1H), 8.01 (*s*, 1H), 7.89 (*s*, 1H), 7.46 (*s*, 1H), 7.24 (*s*, 1H), 3.79 (*s*, 3H), 2.93-2.88 (*m*, 1H), 2.77-2.68 (*m*, 3H), 2.62-2.55 (*m*, 1H), 2.30 (*s*, 3H), 1.42 (*s*, 3H), 1.35 (*s*, 3H). ^{13}C NMR (75 MHz, *pyridine* d_5): δ 175.0 (C), 160.9 (C), 147.4 (C), 147.0 (C), 137.2 (C), 130.4 (CH), 124.8 (C), 121.7 (C), 118.3 (CH), 113.6 (CH), 111.3 (CH), 108.4 (CH), 86.0 (C), 55.5 (CH_3), 47.1 (CH), 35.2 (CH_2), 27.6 (CH_2), 27.6 (CH_3), 22.2 (CH_3), 11.4 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{20}H_{23}N_2O_3S$ 371.4732, obsd. 371.4726.

2.2e 4-[6-(3,4-Dimethoxy-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-ylmethyl]-5,5-dimethyl-dihydro-furan-2-one ***(5e):*** White ppts. (0.026 g, 12 %); m. pt. 206-208 °C; $[\alpha]_D^{27}$ -111.6° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, MeOD): δ 7.89 (*s*, 1H), 7.42 (*s*, 1H), 7.38 (*d*, 1H, *J*=8.3), 7.01 (*d*, 1H, *J*=8.3), 3.90 (*s*, 3H), 3.86 (*s*, 3H), 2.86-2.79 (*m*, 1H), 2.67-2.62 (*m*, 2H), 2.58-2.42 (*m*, 1H), 2.37-2.35 (*m*, 1H), 2.31 (*s*, 3H), 1.49 (*s*, 3H), 1.35 (*s*, 3H). ^{13}C NMR (75 MHz, MeOD): 176.5 (C), 149.7 (C), 149.1(C), 147.2 (C), 146.5 (C), 127.4 (C), 125.1 (C), 121.7 (C), 117.9 (C), 112.3 (C), 109.3 (C), 106.8 (C), 87.0 (C), 55.5 ($2CH_3$), 46.9 (CH), 34.5 (CH_2), 27.0 (CH_2), 26.7 (CH_3), 21.1 (CH_3), 10.3 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{21}H_{25}N_2O_4S$ 401.9992, obsd. 401.9996.

2.2f 4-[6-(3-Hydroxy-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-ylmethyl]-5,5-dimethyl-dihydro-furan-2-one ***(5f):*** White ppts. (0.128 g, 49 %);m. pt. 221-223 °C; $[\alpha]_D^{27}$ -103.6° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, *pyridine* d_5): δ 8.17 (*s*, 1H), 8.02 (*s*, 1H), 7.79-7.77 (*m*, 1H), 7.47-7.42 (*m*, 1H), 7.18 (*s*, 1H), 2.82-2.74 (*m*, 3H), 2.71-2.64 (*m*, 1H), 2.59-2.56 (*m*, 1H), 2.18 (*s*, 3H), 1.34 (*s*, 3H), 1.27 (*s*, 3H). ^{13}C NMR (75 MHz, *pyridine* d_5): δ 174.7 (C), 159.5 (C), 147.3 (C), 147.1 (C), 137.1 (CH), 130.4 (CH), 124.4 (C), 121.3 (C), 116.7 (CH), 115.2 (CH), 113.3 (C), 107.8 (CH), 85.6 (C), 46.8

(CH), 34.9 (CH_2), 27.4 (CH_2), 27.3 (CH_3), 21.9 (CH_3), 11.0 (CH_3).

HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{19}H_{21}N_2O_3S$ 357.4466, obsd. 357.4461.

*2.2g 4-[6-(4-Hydroxy-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-ylmethyl]-5,5-dimethyl-dihydro-furan-2-one (**5g**):* White ppts. (0.026 g, 10 %); m. pt. 207-209 °C; $[\alpha]_D^{27}$ -101.7° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, MeOD): δ 7.65 (*d*, 1H, *J*=8.5), 7.42 (*s*, 1H), 6.85 (*d*, 1H, *J*=8.5), 2.85-2.77 (*m*, 1H), 2.65-2.60 (*m*, 2H), 2.55-2.45 (*m*, 1H), 2.37-2.35 (*m*, 1H), 2.33 (*s*, 3H), 1.48 (*s*, 3H), 1.37 (*s*, 3H). ^{13}C NMR (75 MHz, MeOD): δ 176.5 (C), 162.1 (C), 149.2 (C), 149.1 (C), 129.4 (C), 126.5 (2CH), 124.1 (C), 120.9 (CH), 115.4 (2CH), 105.6 (CH), 87.0 (C), 47.1 (CH), 34.5 (CH_2), 27.0 (CH_2), 26.7 (CH_3), 22.7 (CH_3), 10.2 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{19}H_{21}N_2O_3S$ 357.4466, obsd. 357.4439.

*2.2h 4-[6-(4-Chloro-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-ylmethyl]-5,5-dimethyl-dihydro-furan-2-one (**5i**):* White ppts. (0.995 g, 41 %); m. pt. 212-214 °C; $[\alpha]_D^{27}$ -98.9° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (*d*, 2H, *J*=8.4 Hz), 7.57 (*s*, 1H), 7.39 (*d*, 2H, *J*=8.4 Hz), 2.95-2.85 (*m*, 1H), 2.76-2.67 (*m*, 3H), 2.60-2.45 (*m*, 1H), 2.39 (*s*, 3H), 1.52 (*s*, 3H), 1.41 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (C), 147.2 (C), 136.2 (C), 133.4 (C), 133.3 (C) 129.2 (2CH), 126.7 (2CH), 124.1 (C), 121.7 (C), 106.8 (CH), 86.2 (C), 46.8 (CH), 35.1 (CH_2), 30.1 (CH_2), 28.0 (CH_3), 22.6 (CH_3), 11.9 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{19}H_{20}ClN_2O_2S$ 375.8923, obsd. 375.8947.

*2.2i 4-[6-(4-Bromo-phenyl)-3-methyl-imidazo[2,1-b]thiazol-2-ylmethyl]-5,5-dimethyl-dihydro-furan-2-one (**5j**):* White ppts. (0.107 g, 51 %); m. pt. 212-214 °C; $[\alpha]_D^{27}$ -110.3° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, *pyridine* d_5): δ 8.13 (*d*, 2H, *J*=9Hz), 8.08 (*s*, 1H), 7.69 (*d*, 2H, *J*=9Hz), 2.89-2.78 (*m*, 1H), 2.76-2.69 (*m*, 2H), 2.66-2.60 (*m*, 1H), 2.57-2.50 (*m*, 1H), 2.30 (*s*, 3H), 1.43 (*s*, 3H), 1.35 (*s*, 3H). ^{13}C NMR (75 MHz, *pyridine* d_5): δ 176.4 (C), 149.1 (C), 147.3 (C), 136.2 (2C), 133.8 (2CH), 128.9 (2 CH), 126.1 (C), 123.4 (C), 122.5 (C), 109.8 (CH), 87.3 (C), 48.5 (CH), 36.6 (CH_2), 29.0 (CH_2), 29.0 (CH_3), 23.6 (CH_3), 12.7 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{19}H_{20}BrN_2O_2S$ 420.3433, obsd. 420.3432.

*2.2j 5,5-Dimethyl-4-[3-methyl-6-(4-nitro-phenyl)-imidazo[2,1-b]thiazol-2-ylmethyl]-dihydro-furan-2-one (**5k**):* White ppts. (0.090 g, 39 %); m. pt. 223-225 °C; $[\alpha]_D^{27}$ -108.7° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15-8.13 (*d*, 2H, *J*=6 Hz), 8.08-8.06 (*d*, 2H, *J*=6 Hz), 7.71 (*s*, 1H), 2.93-2.88 (*m*, 1H), 2.76-2.68 (*m*, 2H), 2.56-2.55 (*m*, 1H), 2.40 (*s*, 3H), 1.51 (*s*, 3H), 1.40 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (C), 149.0 (C), 148.1 (C), 144.9 (C), 136.3 (C), 131.2 (CH), 130.0 (CH), 124.2 (C), 122.3 (CH), 122.1 (CH), 120.1 (C), 107.9 (CH), 86.2 (C), 46.8 (CH), 35.1 (CH_2), 28.0 (CH_3), 28.0 (CH_2), 22.5 (CH_3), 11.8 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{19}H_{20}N_3O_4S$ 386.4448, obsd. 386.4439.

*2.2k 5,5-Dimethyl-4-[3-methyl-6-(3-nitro-phenyl)-imidazo[2,1-b]thiazol-2-ylmethyl]-dihydro-furan-2-one (**5l**):* Off white ppts. (0.053 g, 23 %); m.pt. 213-215 °C; $[\alpha]_D^{27}$ -118.7° (*c*=0.01, MeOH). ^{1}H NMR (300 MHz, MeOD): δ 8.71 (*s,* 1H), 8.24 (*s,* 1H), 7.93 (*s,* 1H), 7.71-7.65 (*m,* 2H), 2.90-2.87 (*m,* 1H), 2.74-2.69 (*m,* 2H), 2.56-2.55 (*m,* 1H), 2.51 (*s,* 3H), 1.55 (*s,* 3H), 1.46 (*s,* 3H).^{13}CNMR (75 MHz, MeOD): δ 174.9 (C), 147.7 (C), 147.6 (C), 143.9 (C), 134.5 (C), 129.3 (CH), 128.5 (CH), 123.2 (C), 121.3 (CH_2), 120.5 (C), 118.0 (CH), 107.6 (CH),

85.5 (C), 46.2 (CH), 33.0 (CH_2), 28.2 (CH_2), 27.9 (CH_3), 22.6 (CH_3), 11.9 (CH_3). HRMS (ESI) data: m/z calcd. for $[M+H]^+$ $C_{19}H_{20}N_3O_4S$ 386.4448, obsd. 386.4436.

2.3 Physicochemical prediction

For the prediction of physicochemical properties, Lipinski rule of five was performed using molinspiration online program (http://www.molinspiration.com/). "Lipinski Rule of Five" is a rule of thumb to evaluate drug likeness or determine that if a compound is more likely to be membrane permeable and easily absorbed by the body.

3. Results and Discussion

A milder regioselective process has been developed for the synthesis of γ-butyrolactone substituted imidazothiazoles **5a-5l** starting from thiazole amine (**4**) and α-bromo acetophenone derivatives. Thiazole amine was prepared as described in our previous report[18]. Different substituted α-bromo acetophenones (**3a-3l**), were prepared using catalytic quantity of anhydrous $AlCl_3$ for selective and complete conversion (Scheme 1) from their corresponding acetophenones. These derivatives were further expended for the synthesis of γ-butyrolactone substituted imidazo[2,1-b][1,3]thiazoles, and the desired products were formed in low to moderate yields.

To see the effect of functional groups, different substitutions with benzene ring of α-bromo acetophenone were employed (Table 1). Electron rich aromatic ketones generally gave higher yields (entries 1-4) of products 5a-5d. No significant effect of position of $–OCH_3$ (meta and para) in acetophenones were observed to improve the yield. The –OH group at meta- position acts as electron withdrawing in nature, hence the low relative yield of 5f was recorded. In case of *di*-OH substituted acetophenone derivative (entry 8, Table 1), a number of products were observed on TLC during the bromination step, therefore, the desired product was not formed with *di*-OH substituted acetophenone. In case of halogens, the chlorine substituted acetophenone afforded 5i comparably in lesser amount than the bromo substituted acetophenone 5j. Strongly electron withdrawing substituents like $–NO_2$ yielded least conversion of 5k (39%, entry 11) and 5l (20%, entry 12). Although nitro substituted imidazo[2,1-b]thiazole derivatives of γ-butyrolactone are interesting molecules for further modifications but poor conversions of 5k and 5l (39 and 20%) were observed which limits the process.

Scheme 1 for the synthesis of imidazo[2,1-b]thiazole fused γ-butyrolactone derivatives 5a-5l.

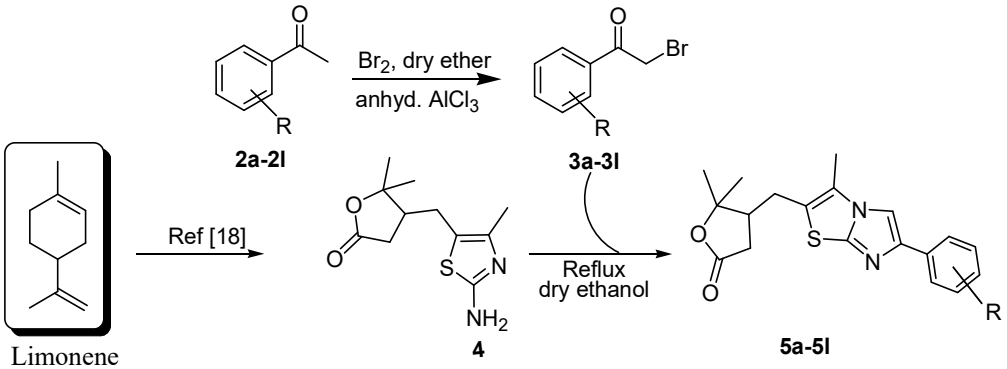
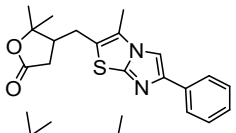
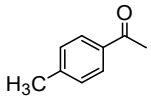
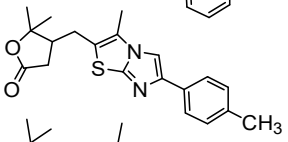
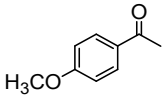
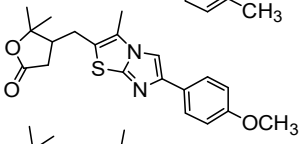
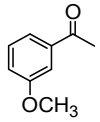
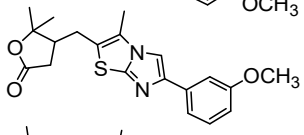
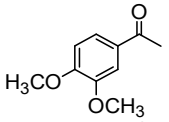
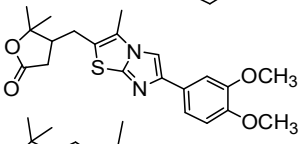
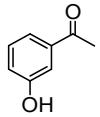
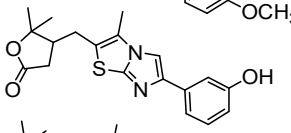
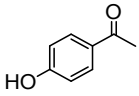
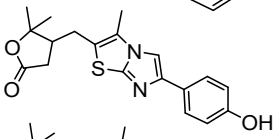
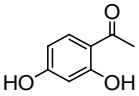
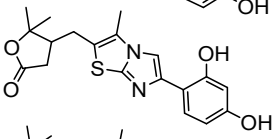
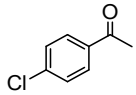
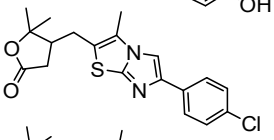
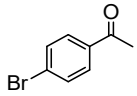
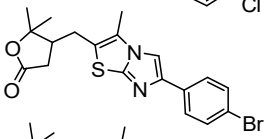
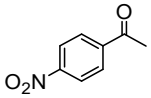
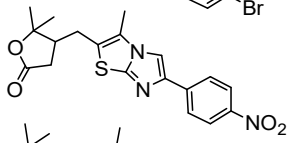
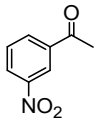
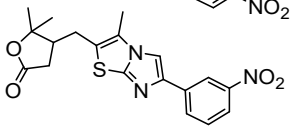


Table 1. Different substituted imidazo[2,1-b]thiazole fused γ-butyrolactone derivatives 5a-5l.

Entry	Acetophenon derivatives	time (h)	Product[a]		Overall yield (%)[b]
1		24		**5a**	59
2		24		**5b**	55
3		24		**5c**	57
4		24		**5d**	53
5		24		**5e**	12
6		24		**5f**	49
7		24		**5g**	10
8		24		**5h**	nd[c]
9		24		**5i**	41
10		24		**5j**	51
11		24		**5k**	39
12		24		**5l**	23

[a]All products were characterized by ^{1}H NMR, ^{13}C NMR and HRMS (ESI) spectral data. [b]Isolated yields were calculated from **4.** [c]nd: not detected.

4. Conclusion

In this study, a series of synthesized compounds (5a–5l) were screened using Mol inspiration property engine v2013.09 to predict the physicochemical parameters (Table 2). The standard values for these properties are given in parentheses i.e., molecular weight (160-480 g/mol), partition coefficient (-0.4 - 5.6), total polar surface area (<60

angstroms), hydrogen bond donor (<5), hydrogen-bond acceptor (<10). When the values for physicochemical parameters lies out of the given limits, that compound violates the 'Lipinski rule of Five' and thus the number of violations are termed as Lipinski score. The results revealed that all compounds were following the "Lipinski Rule of Five." Hence on the basis of above physicochemical properties (Table 2) of the synthesized heterocyclic molecules, these could be expected as good drug candidates.

Table 2. Computational database of imidazo[2,1-b]thiazole fused γ-butyrolactone derivatives

Sample	MW[a]	MV[b]	Log P[c]	TPSA[d]	HBD[e]	HBA[f]	Lipinski score[g]
5a	340.44	305.11	2.84	43.61	0	4	0
5b	354.47	321.67	3.29	43.61	0	4	0
5c	370.47	330.65	2.90	52.84	0	5	0
5d	370.47	330.65	2.87	52.84	0	5	0
5e	400.50	356.20	2.49	62.00	0	6	0
5f	356.44	313.12	2.34	63.84	1	5	0
5g	356.44	313.12	2.36	63.84	1	5	0
5h	372.44	321.14	2.07	84.06	2	6	0
5i	374.89	318.64	3.52	43.61	0	4	0
5j	419.34	322.99	3.65	43.61	0	4	0
5k	385.44	328.44	2.80	89.43	0	7	0
5l	385.44	328.44	2.77	89.43	0	7	0
Levamisole	204.30	183.77	2.01	15.60	0	2	0

[a]molecular weight, [b]molecular volume, [c]partition coefficient, [d]total polar surface area, [e]hydrogen-bond donor, [f]hydrogen-bond acceptor, [g]number of unmet criteria of Lipinski Rule of Five.

In summary, a method to synthesize diverse set of γ-butyrolactone substituted imidazo[2,1-b][1,3]-thiazole have been developed. The selective bromination of different acetophenone derivatives followed by the reaction with previously prepared thiazole amine led to the formation of different substituted γ-butyrolactone fused heterocyclic imidazo[2,1-b][1,3]-thiazoles. The interesting hybrid structures of γ-butyrolactone hybrid imidazo[2,1-b][1,3]-thiazoles could attract the attention of researchers for finding new biological activities.

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