Chemistry & Biology Interface, 2021, 11, 5, 160-165

RESEARCH PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Design, Synthesis and Pharmacokinetic Evaluation of Novel Water Soluble Celecoxib Prodrugs†

Pradip K. Sasmal*[a], LeZhen Li,[b] Qingqi Liu[b]

[a]*Proprietary Products, Dr. Reddy's Laboratories Ltd., Bachupally, Hyderabad 500090, India*
[b]*Pharmaron Beijing Co., Ltd., 6 Taihe Road; BDA, Beijing 100176, China*
**Corresponding author: Tel. +91 40 4434 6865; e-mail: pradipks@drreddys.com*

† DRL Publication No. 876
Received; 6 September 2021, Accepted; 14 October 2021

Abstract: Celecoxib is practically insoluble in water and due to this aqueous solubility limitation, development of injectable celecoxib products become extremely challenging. We focused our efforts to develop water soluble injectable celecoxib prodrugs which could be used acutely in hospital settings for various pain management. The design, synthesis and pharmacokinetic evaluation of novel celecoxib prodrugs are described herein. One lead prodrug with high water solubility and good pharmacokinetic profile was identified for further development.

Key-words: Celecoxib, Prodrugs design, Solubility, Pharmacokinetic profile

INTRODUCTION: Prodrugapproach is one of the important tools to medicinal chemists to convert good molecules to better drugs [1-3]. Many widely used pharmaceuticals have been developed as prodrugs and approximately 10% of all drugs [4] approved globally are prodrugs.

COX-2 inhibitors are a class of drugs used for the treatment of pain and inflammation such as rheumatoid arthritis, ankylosing spondylitis, acute pain, and osteoarthritis [5-7]. So far, only three COX-2 inhibitors e.g., celecoxib, rofecoxib and valdecoxib (Figure 1) have been approved by various regulatory agencies. Amongst these, only celecoxib is available in US market. Parecoxib [8] (Figure 1), a water-soluble and injectable prodrug of valdecoxib, is available in the European Union and can be used for short term perioperative pain control when patients are unable to take oral medications [9-11]. Over the years many researchers have reported different types of celecoxib prodrugs [12-18] to address specific drug delivery objectives via oral route of administration. Celecoxib is practically insoluble in water and thus pose challenges to develop aqueous based injectable celecoxib products. Our focus was to synthesize water soluble celecoxib prodrugs which could be developed easily as injectable products and used acutely in hospital settings for various pain

management. We describe herein our approach to design and synthesize celecoxib prodrugs and pharmacokinetic profile of these compounds.

RESULTS AND DISCUSSION: The sulfonamide functionality in celecoxib offers handle for prodrug design. We explored three strategies to convert amino part of sulfonamide into a) N-phosphates, b) amides and c) carbamates. To enhance aqueous solubility, amides and carbamates were further attached to phosphate or sugar tail groups via suitable linkers. In few cases phosphate group was converted to corresponding sodium salts to boost further solubility, ensure better handling and long term stability at room temperature. Structures of these prodrugs **5-13** are mentioned in Figure 2.

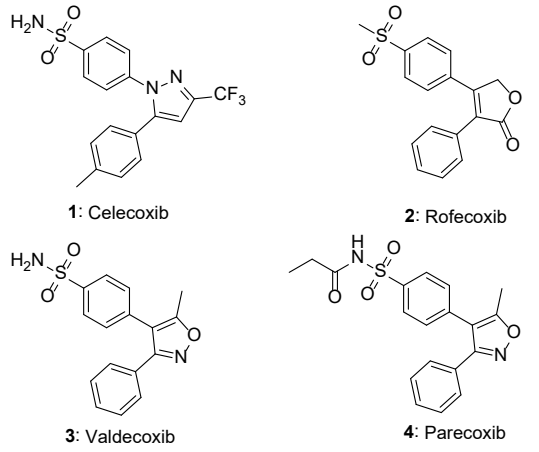


Figure 1. Structures of COX2 inhibitors

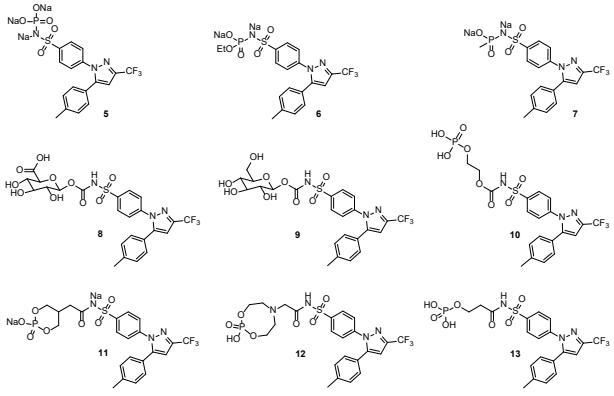
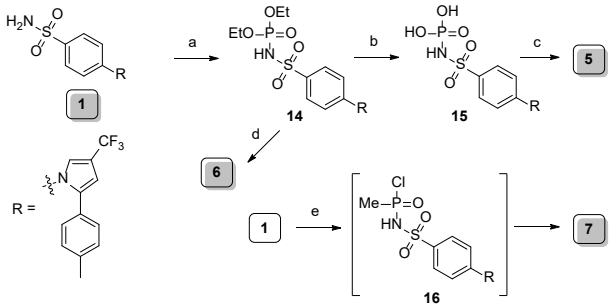
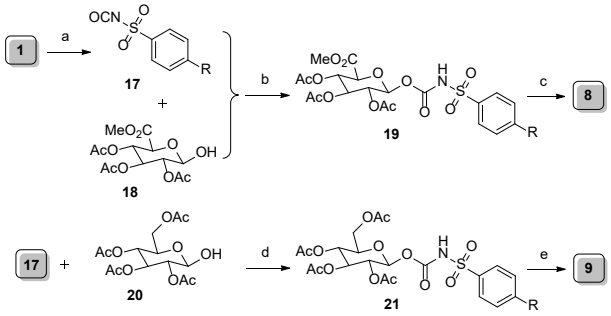


Figure 2. Structures of celecoxib prodrugs (**5-13**)

The target compounds were synthesized as outlined in Schemes 1-5. The synthesis of compound **5** was commenced with the phosphorylation of celecoxib with diethyl chlorophosphate to produce compound **14** (Scheme 1). Treatment of **14** with trimethylsilyl iodide led to the formation of acid **15** which was converted to the desired compound **5** as sodium salt. Compound **14** on treatment with sodium iodide followed by sodium hydroxide furnished compound **6**. Reaction of celecoxib with methylphosphonic dichloride produced *in situ* intermediate **16** which on treatment with sodium hydroxide afforded desired compound **7**. For the synthesis of sugar-appended carbamoyl prodrugs **8** and **9**, first celecoxib was reacted with chlorosulfonyl isocyanate to form sulfonyl isocyanate intermediate **17**. Reaction between **17** and **18** [19] provided methyl ester **19** which upon hydrolysis gave desired target compound**8**. In a similar manner compound **17** on treatment with **20** [20] afforded **21** which was subsequently converted to target compound **9** (Scheme 2).

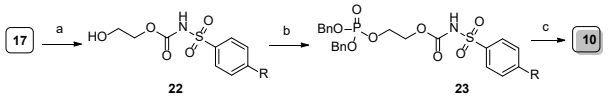


Scheme 1. Reagents and conditions: (a) diethyl chlorophosphate, 1N NaOH, THF, 0°C to RT, 1h, 80%, (b) Me_3SiI, CH_3CN, 0°C, 1h, 38%, (c) Aqueous 0.5N NaOH, RT, 1h, 23%, (d) NaI, acetone, reflux, 16h, followed by 1N NaOH, DMSO, 1h, prep-HPLC, 10%, (e) methylphosphonic dichloride, TEA, DCM, RT, 16h, followed by aqueous 1N NaOH, RT, 2h, prep-HPLC, 18%.



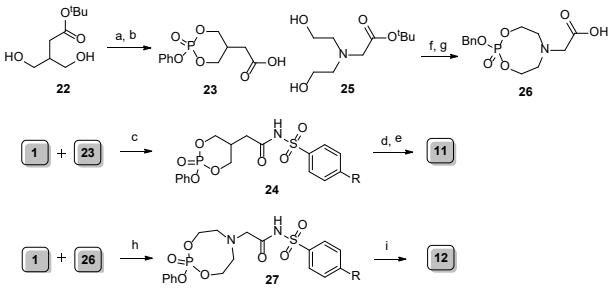
Scheme 2. Reagents and conditions: (a) $ClSO_2NCO$, benzene, 80 °C, 3h, 100% (crude), (b) DABCO, toluene, RT, 5h, 50%, (c) LiOH, MeOH-THF-water, RT, 2h, prep-HPLC, 20%, (d) DABCO, toluene, RT, 5h, 40%, (e) LiOH, MeOH-THF-water, RT, 2h, prep-HPLC, 25%.

Reaction of ethylene glycol with sulfonyl isocyanate **17** furnished 2-hydroxyethyl sulfonylcarbamate derivative **22**. The primary hydroxyl group within **22** was reacted with dibenzyl N,N-diisopropylphosphoramidite followed by oxidation with hydrogen peroxide to afford intermediate **23**. Hydrogenolytic cleavage of benzyl groups within **23** produced phosphate prodrug **10** (Scheme 3).

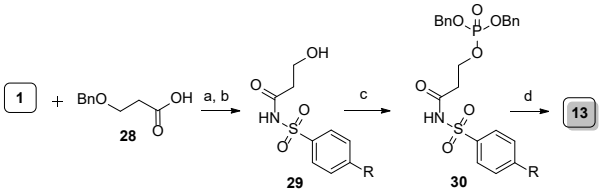


Scheme 3. Reagents and conditions: (a) ethylene glycol, N-methylmorpholine, THF, 0°C to RT, 2h, 59%, (b) dibenzyl N,N-diisopropylphosphoramidite, 1H-tetrazole, DCM, 0°C to RT, 1h, followed by H_2O_2, 0°C to RT, 1h, 26%, (c) Pd/C, H_2, MeOH, RT, 16h, prep-HPLC, 16%.

For the synthesis of prodrugs **11-13**, the primary sulfonamide moiety of celecoxib was coupled with suitable carboxylic acids to provide N-acyl sulfonamide functionality. The coupling of tert-butyl 4-hydroxy-3-(hydroxymethyl) butanoate (**22)** [21] with phenoxyphosphonoyl dichloride followed by trimethylamine mediated hydrolysis of t-butyl ester afforded carboxylic acid **23**. Following similar sequence of reactions, carboxylic acid **26** was obtained from diol **25** [22]. The EDCI/DMAP mediated coupling of acid **23** with celecoxib followed by hydrogenolysis of phenyl phosphate esters by Adams' catalyst (PtO_2) and salt formation with NaOH furnished prodrug **11**. Similarly coupling of compound **26** with celecoxib followed by hydrogenolysis with Adams' catalyst afforded desired compound **12** (Scheme 4).



Scheme 4. Reagents and conditions: (a) phenoxyphosphonoyl dichloride, TEA, DCM, 0°C to RT, 2h, 59%, (b) TFA, DCM, RT, 3h, 88%, (c) EDCI, DMAP, $CHCl_3$, 60 °C, 12h, 19%, (d) PtO_2, H_2, DCM, RT, 12h, 38%, (e) NaOH, MeOH, RT, 2h, prep-HPLC, 33%, (f) phenoxyphosphonoyl dichloride, TEA, DCM, 0°C to RT, 16h, 41%, (g) TFA, DCM, RT, 16h, 100% (crude), (h) EDCI, DMAP, $CHCl_3$, 60 °C, 12h, 25%, (i) PtO_2, H_2, iPrOH, 60 °C, 16h, prep-HPLC, 11%.



Scheme 5. Reagents and conditions: (a) HATU, DIEA, DMF, RT, 6h, 70%, (b) 10% Pd/C, H_2, THF, RT, 12h, 96%, (c) dibenzyl N, N-diisopropylphosphoramidite, 1H-tetrazole, DCM, RT, 1h, followed by H_2O_2, 0°C to RT, 30 min, 64%, (d) 10% Pd/C, H_2, MeOH, RT, 12h, prep-HPLC, 32%.

Coupling of 3-(benzyloxy)propanoic acid (**28)** [23] with celecoxib followed by O-debenzylation afforded compound **29** (Scheme 5). The hydroxyl functionality was treated with dibenzyl N,N-diisopropylphosphoramidite

followed by oxidation with hydrogen peroxide afforded dibenzyl phosphate derivative **30**. Hydrogenolytic cleavage of dibenzyl phosphate furnished compound **13**.

Table 1. Solubility profile of celecoxib prodrugs (**5-13**) at PBS buffer @pH 7.4 at 25°C.

Entry	Compound	Solubility at PBS buffer @ pH 7.4 (mg/mL)		Theoretical amount of celecoxib @24 h (mg/mL)
		4 h	24 h	
1	**1**	0.0004	0.0004	0.0004
2	**5**	72	80	58
3	**6**	73	76	57
4	**7**	131	125	89
5	**8**	96	111	70
6	**9**	105	115	74
7	**10**	89	91	63
8	**11**	106	97	61
9	**12**	88	96	62
10	**13**	99	108	77

Having compounds **5-13** in hand the next course of work was to check the solubility of these compounds in PBS buffer @pH 7.4 after 4 h and 24 h at 25°C (Table 1). The thermodynamic solubility at 24 h was found to be more or less similar to their kinetic solubility at 4 h. The solubility data clearly indicates that all these prodrugs have shown significantly higher solubility of 76-125 mg/mL (which is equivalent to 57-89 mg/mL of celecoxib) in aqueous media compared to the solubility of the parent drug celecoxib (0.0004 mg/mL).

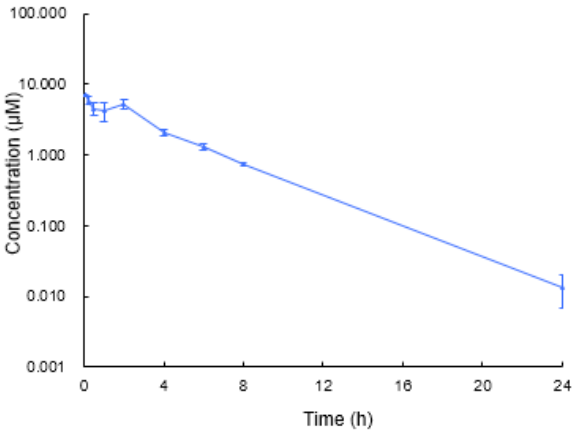


Figure 3. Plasma PK profile of compound **5** in SD rats

At this juncture, it was important to understand the *in vivo* biotransformation of prodrugs to deliver parent active molecule celecoxib by enzymatic and chemical cleavages of linkers and pro-moieties. For the treatment of acute pain, prodrugs need to cleave as fast as possible producing parent active compound. All synthesized prodrugs **5-13** were dosed intravenously (IV) in rats @10 mg/kg celecoxib equivalent dose and the parent drug celecoxib was monitored in the plasma [24]. The pharmacokinetic profile of these compounds

Table 2. Pharmacokinetic profile of prodrugs **5-13** in SD rats via IV route of administration

Entry	Compound	Mol Wt	Mol Wt ratio (Prodrug to Celecoxib)	Dose (mg/kg)	t1/2 (h)	Tmax (h)	Cmax (µM)	AUClast (µM*h)
1	**1**	381.37	1.00	10.0	4.1	0	8.46	54.70
2	**5**	527.30	1.38	13.8	2.7	0	7.79	28.90
3	**6**	503.34	1.32	13.2	4.6	0.25	4.75	31.40
4	**7**	533.37	1.40	14.0	17.2	8	0.34	6.00
5	**8**	601.51	1.58	15.8	4.4	6	1.95	26.80
6	**9**	587.52	1.54	15.4	5.6	2	2.05	23.50
7	**10**	549.41	1.44	14.4	7.0	0	0.38	1.57
8	**11**	603.42	1.58	15.8	6.2	0	0.55	2.58
9	**12**	588.49	1.54	15.4	8.7	8	1.01	14.40
10	**13**	533.41	1.40	14.0	3.9	2.5	1.51	15.10

are summarized in Table 2. Comparing AUClast (AUC: area under the curve) between celecoxib and prodrugs, compounds **7**, **10-13** showed significantly lower celecoxib levels across time points. Compounds **5**, **6**, **8** and **9** have shown reasonably better overall exposure (AUC wise) of celecoxib. Amongst these four prodrugs, compounds **8** and **9** have shown very low Cmax (Cmax: maximal concentration in the plasma) with higher Tmax (Tmax: time to reach maximal concentration). Compound **6** also showed good overall exposure but Cmax was more blunted at 4.75 μM with Tmax of 15 min. The fastest release of the parent drug celecoxib from prodrugs was observed with compound **5**. The PK data indicates that the release of parent drug celecoxib happened instantaneously from prodrug **5** and also it has shown comparable Cmax to that of compound **1** (7.79 μM vs 8.46 μM). Though there was little reduction in overall exposure, this has relatively lesser concern as acute pain treatment is primarily Cmax driven. Besides, during human clinical studies, the dose volume for the injectable product can be easily adjusted to obtain optimal Cmax and AUC considering difference in drug clearance mechanism between animals and humans.

Considering overall PK profile, prodrug **5** was considered to be the best lead molecule which showed several thousand-fold higher solubility compared to the parent drug celecoxib. The PK profile of compound **5** is presented in Figure 3.

CONCLUSION: In summary, we have synthesized various chemically diverse celecoxib prodrugs [25] using celecoxib as starting material. In general, all these prodrugs have shown significantly higher aqueous solubility compared to the parent drug celecoxib. Compound **5** have shown the acceptable PK profile in rats demonstrating instant release of the drug after IV administration in rats. Further PK studies in humans are required to understand the full potential of this prodrug for the management of acute pain in hospitals. Though in literature different solubilization techniques are reported for celecoxib [26-30], these approaches use different organic solvents, lipids and surfactants as solubilizers and in most of the cases, such solvent cocktail shows both local and systemic safety concerns. The work described in this paper will provide a better option to develop organic solvent free water based celecoxib injection product to address patients' need.

CONFLICT OF INTEREST: The authors confirm that the content of this article has no conflicts of interest.

ACKNOWLEDGEMENTS:

Support and continuous encouragement from the management of Dr. Reddy's Laboratories Ltd. are highly acknowledged. Support from Pharmaron for the synthesis of compounds is highly appreciated.

REFERENCES AND NOTES:

1. Najjar A, Karaman R. *Expert Opin Drug Discov.* 2019; 14:199-220.
2. Najjar A, Karaman R. *Expert Opin Drug Deliv.* 2018; 18:1-5.
3. Rautio J, Kumpulainen H, Heimbach T, Oliyai R, Oh D, Järvinen T, Savolainen J. *Nat. Rev. Drug Discov*. 2008; 7: 255–270.
4. Rautio J, Meanwell, NA, Di L, Hageman MJ. *Nat Rev Drug Discov.* 2018; 17:559-587.
5. Dancel R, Liles EA, Fiore D. *Rev Recent Clin Trials.* 2017; 12: 277-283.
6. Jain KK. *Expert OpinInvestig Drugs.* 2000; 9: 2717-23.
7. Dalpiaz AS, Peterson D. *Expert Rev Neurother.* 2004; 4: 165-77.
8. Cheer SM, Goa KL. *Drugs*. 2001; 61: 1133-42.
9. Curtis E, Fuggle N, Shaw S, Spooner L, Ntani G, Parsons C, Corp N, Honvo G, Baird J, Maggi S, Dennison E, Bruyère O, Reginster JY, Cooper C. *Drugs Aging.* 2019; 36 (Suppl 1): 25-44.
10. Sharma V, Bhatia P, Alam O, JavedNaim M, Nawaz F, Ahmad Sheikh A, Jha M. *Bioorg Chem.* 2019; 89: 103007-51.
11. Regulski M, Regulska K, Prukała W, Piotrowska H, Stanisz B, Murias M. *Drug Discov Today.* 2016; 21: 598-615.
12. Li Y, Xiao Y, Yin Z. *AAPS PharmSciTech.* 2017; 18: 729-737.
13. Lee S, Lee Y, Kim W, Nam J, Jeong S, Yoo JW, Kim MS, Moon HR, Jung Y. *Drug Des DevelTher.* 2015; 9: 4227-37.
14. Marquez Ruiz JF, Kedziora K, Pigott M, Keogh B, Windle

H, Gavin J, Kelleher DP, Gilmer JF. *Bioorg Med Chem Lett.* 2013; 23: 1693-8.
15. Lee Y, Kim J, Kim H, Kang S, Yoon JH, Kim DD, Kim YM, Jung Y. *J Pharm Sci.* 2012; 101: 1831-42.
16. Malik P, Kadam RS, Cheruvu NP, Kompella UB. *Mol Pharm.* 2012; 9: 605-14.
17. Ruiz JF, Kedziora K, Keogh B, Maguire J, Reilly M, Windle H, Kelleher DP, Gilmer JF. *Bioorg Med Chem Lett.* 2011; 21: 6636-40.
18. Chowdhury MA, Abdellatif KR, Dong Y, Yu G, Huang Z, Rahman M, Das D, Velázquez CA, Suresh MR, Knaus EE. *Bioorg Med Chem Lett.* 2010; 20: 1324-9.
19. Asami Y, Kawaguchi Y, Kanie Y, Abdu-Allah H, Suzuki K, Kanie O. *Carbohydrate Research*, 2019; 474: 51-56.
20. Hayes JA, Eccles KS, Lawrence SE, Moynihan HA. *Carbohydrate Research*, 2012; 349: 108-112.
21. Adam J-M, Foricher J, Hanlon S, Lohri B, Moine G, Schmid R, Stahr H, Weber M, Wirz B, Zutter U. *Organic Process Research & Development,* 2011; 15: 515-526.
22. Greenwald RB, Zhao H, Yang K, Reddy P, Martinez A. *J. Med. Chem.* 2004; 47: 726-734.
23. Ahmed MS, Mannel DS, Root TW, Stahl SS. *Organic Process Research & Development,* 2017; 21: 1388-93.
24. All rat studies were performed in compliance with the policy on animal use and ethics.
25. Characterization data of compound **5**: ^{1}H NMR (300 MHz, CD_3OD):δ8.09 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.10-7.28 (m, 4H), 6.89 (s, 1H), 2.35 (s, 3H). LCMS (ES, m/z): 460.0 [M-H]; compound **6**: ^{1}H NMR (300 MHz, DMSO-d_6):δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.16 (s, 4H), 7.12 (s, 1H), 3.48-3.46 (m, 2H), 2.27 (s, 3H), 0.86-0.84 (m, 3H); LCMS (m/z): 490 (M-2Na+3H); compound **7**: ^{1}H NMR (400 MHz, DMSO-d_6):δ7.87 (d, *J* = 8.0 Hz, 2H), 7.21 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.15-7.00 (m, 4H), 2.21 (s, 3H), 0.81 (d, , *J* = 15.6 Hz, 3H); LCMS (ES, *m/z*): 458 (M-2Na+H); compound **8**: ^{1}H NMR (300 MHz, DMSO-d_6): δ7.78 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.25-7.15 (m, 4H), 7.15 (s, 1H), 7.15-6.86 (br m, 2H), 5.05-4.85 (m, 2H), 3.20-3.05 (m, 2H), 3.05-2.95 (m, 1H), 2.31 (s, 1H); LCMS (ES, *m/z*): 602 [M+H]; compound **9**: ^{1}H NMR (400 MHz, DMSO-d_6):δ7.77 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.23-7.16 (m, 4H), 7.15 (s, 1H), 5.04-5.00 (m, 2H), 4.89 (d, *J* = 4.5 Hz, 1H), 4.84 (d, *J* = 4.5 Hz, 1H), 4.55 (t, *J* = 6.0 Hz, 1H), 3.62-3.55 (m, 1H), 3.42-3.33 (m, 1H), 3.15-2.95 (m, 4H), 2.31 (s, 3H); LCMS (ES, *m/z*): 610 (M+Na); compound **10**: ^{1}H NMR (400 MHz, DMSO-d_6):δ 12.23 (br s , 1H), 11.30 (br s, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.23-7.18 (m, 5H), 4.16-4.13 (m, 2H), 3.95-3.91 (m, 2H), 2.32 (s, 3H); LCMS (ES, *m/z*): 550 (M+H); compound **11**: ^{1}H NMR (400 MHz, CD_3OD): δ8.07 (d, *J* = 8.2 Hz,2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.26-7.19 (m, 4H),6.93 (s, 1H), 4.11-4.07 (m, 1H), 3.92-3.82 (m, 2H), 3.82-3.76 (m, 1H), 2.82-2.71 (m, 1H), 2.63-2.56 (m, 1H), 2.48-2.39 (m, 1H), 2.38 (s, 3H); LCMS (ES, *m/z*): 560 (M-2Na+3H); compound **12**: ^{1}H NMR (400 MHz, DMSO-d_6):δ7.94 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.22-7.17 (m, 4H), 7.20 (s, 1H), 3.99-3.93 (m, 4H), 3.56 (s, 2H), 2.92-2.86 (m, 4H), 2.92 (s, 3H); LCMS (ES,*m/z*): 589 (M+H); compound **13**: ^{1}H NMR (400 MHz, CD_3OD): δ7.99 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.24-7.18 (m, 4 H), 6.90 (s, 1 H), 4.15-4.00 (m, 2 H), 2.55 (t, *J* = 6.2 Hz, 2 H), 2.38 (s, 3 H); LCMS (ES, *m/z*): 534 [M+H].
26. Mahapatra APK, Patil V, Patil R. *Int. J. Pharmtech Res.* 2020; 13: 80-93.
27. Jouyban-Gharamaleki V, Soleymani J, Jouyban-Gharamaleki K, Suleymanov TA, Jouyban A. *J. Mol. Liq.* 2017; 243: 715-719.
28. Garti N, Avrahami M, Aserin A. *J Colloid Interface Sci.* 2006; 299: 352-65.
29. Jansook P, Kulsirachote P, Loftsson T. *J. Incl. Phenom. Macrocycl. Chem.* 2018; 90: 75–88.
30. Agrawal S, Soni N, Jain NK, Agrawal GP. *Int. J. Pharm. Sci. Res.* 2012; 3: 2325-36.