Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

A novel approach for the synthesis of functionalized hydroxylamino derivative of dihydroquinazolinones

Chikkanti Jaganmohan, Vinay Kumar K. P., Venkateshwarlu R., Sandeep Mohanty, Jaydeep Kumar, Venkateswara Rao B., Akula Raghunadh & Krishnaji Tadiparthi

To cite this article: Chikkanti Jaganmohan, Vinay Kumar K. P., Venkateshwarlu R., Sandeep Mohanty, Jaydeep Kumar, Venkateswara Rao B., Akula Raghunadh & Krishnaji Tadiparthi (2020): A novel approach for the synthesis of functionalized hydroxylamino derivative of dihydroquinazolinones, Synthetic Communications, DOI: 10.1080/00397911.2020.1768406

To link to this article: https://doi.org/10.1080/00397911.2020.1768406

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2020.1768406

Taylor & Francis
Taylor & Francis Group

A novel approach for the synthesis of functionalized hydroxylamino derivative of dihydroquinazolinones

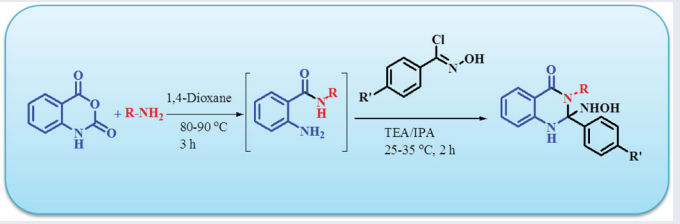
Chikkanti Jaganmohan[a,b], Vinay Kumar K. P.[a], Venkateshwarlu R.[a], Sandeep Mohanty[a], Jaydeep Kumar[a], Venkateswara Rao B.[b], Akula Raghunadh[a], and Krishnaji Tadiparthi[c]

[a]Dr. Reddy's Laboratories Limited, Hyderabad, India; [b]Department of Organic Chemistry and FDW, Andhra University, Visakhapatnam, India; [c]Department of Chemistry, CHRIST (Deemed to be University), Bangalore, India

ABSTRACT

A new metal-free and modular approach for the synthesis of various functionalized dihydroquinazolinones has been developed from isatoic anhydride, amines, 4-chloro-*N*-hydroxybenzimidoylchloride to yield up to 71%. The reaction has been screened in various bases, solvents at different temperatures. The substrate scope of the reaction has been studied with various amines and the possible reaction mechanism for this reaction has also been proposed.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 19 March 2020

KEYWORDS
4-Chloro-*N*-hydroxybenzimidoylchloride; dihydroquinazolinones; isatoic anhydride

Introduction

Because of the structural diversification, heterocyclic chemistry has always been a challenging and emerging area of research for pharmaceutical industry.[1] Indeed, these compounds are showing the intrinsic biological activity in the toxicological studies and

CONTACT Akula Raghunadh rgkraghu@gmail.com Dr. Reddy's Laboratories Limited, Hyderabad 500049, India; Krishnaji Tadiparthi krishnaji.tadiparthi@christuniversity.in Department of Chemistry, CHRIST (Deemed to be University), Hosur Road, Bangalore 560029, India.

Supplemental data for this article can be accessed on the publisher's website

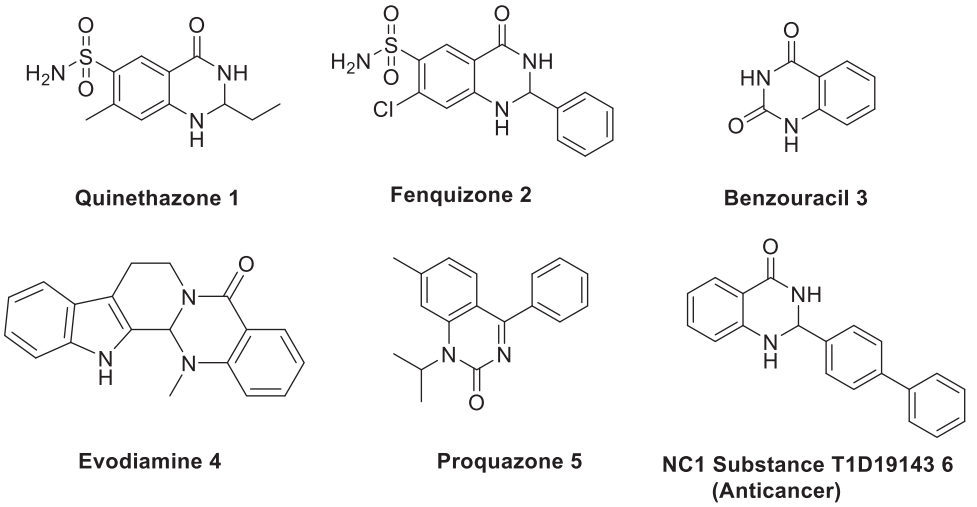


Figure 1. Some important biologically important dihydroquinazolinones compounds.

clinical studies. Notably, the innovative companies like AstraZeneca, Pfizer are affording substantial effort to find the novel molecules like AZD1390, AZD2811, Capivasertib and Adriatic.[2] Indeed, during the past decade, an aggressive research on heterocyclic chemistry has been developed especially after invention of Heck, Suzuki and Negishi coupling reactions.[3] Notably, dihydroquinazolinones are one among them present in various biologically active molecules like Quinethazone (**1**), Fenquizone (**2**), Benzouracil (**3**), Evodiamine (**4**), Proquazone (**5**) and NC1 Substance T1D19143 (**6**) (Figure 1). However, these compounds having immense potential therapeutic properties against anti-cancer, antidiabatic, antihypertension, anticonvelsant, and antianxieticactivities.[4–12]

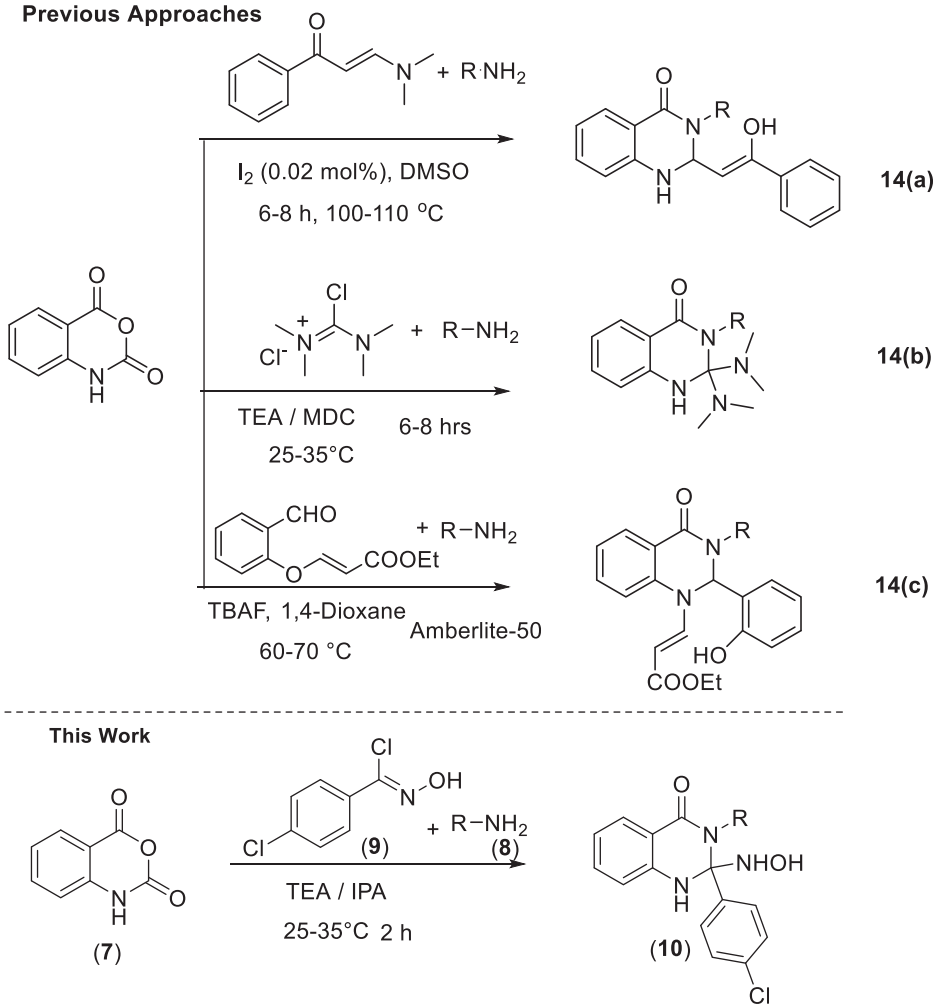
Inspite of their biological activity and various applications in organic chemistry, a good number of publications and patents have been reported.[13] Moreover, this has stimulated us for the development of various functionalized dihydroquinazolinones by different strategies. However, the invention of novel molecules with reliability, efficiency, and elegant approach is always a challenging and encouraging in organic chemistry

Results and discussion

In continuation of our earlier efforts for the preparation of various biologically active heterocyclic compounds (Scheme 1),[14] herein, we report a novel functionalized synthesis of dihydroquinazolinones starting from commercially available isatoic anhydride.

The syntheses of various dihydroquinazolinones have been prepared by taking isatoic anhydride, 4-chloro-*N*-hydroxybenzimidoylchloride with various amines. Initially, the reaction conditions were optimized by taking isatoic anhydride, 4-chloro-*N*-hydroxybenzimidoylchloride with cyclopropyl amine as model substrates.

The reaction has been screened in various solvents like DCM, $CHCl_3$, IPA, DMF, and THF with a combination of different bases like Et_3N, $NaHCO_3$ at different



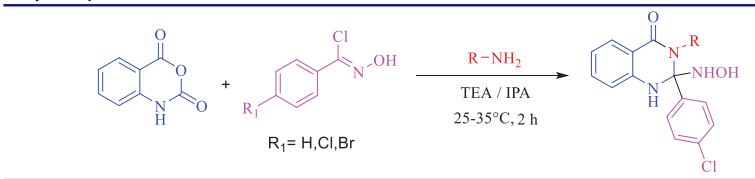
Scheme 1. Different approaches for the synthesis of dihydroquinazolinone derivatives.

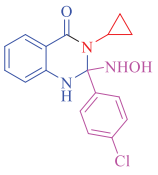
Table 1. Optimization of reaction conditions.

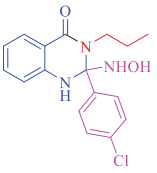
Solvent	Temperature (°C)	Base (eq.)	Time (hr)	Yield (%)
DCM	35	TEA (1)	3	40
DCM	40	TEA (1)	2	40
DCM	45	TEA (2)	3	45
Chloroform	35	TEA (2)	3	46
Chloroform	60	$NaHCO_3$ (2)	3	48
IPA	35	TEA (1)	2	55
IPA	35	TEA (2)	2	65
IPA	**35**	**TEA (2.5)**	**2**	**70**
IPA	35	TEA (2.5)	4	60
IPA	85	TEA (2.5)	2	50
IPA	35	$NaHCO_3$ (2.5)	3	55
DMF	35	TEA (2.5)	3	65
THF	35	TEA (2.5)	3	65
IPA	35	TEA.HCl (3)	2	50
IPA	35	No base	3	30
No solvent	35	TEA (1)	2	45

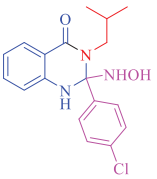
Bold values represents final optimum conditions.

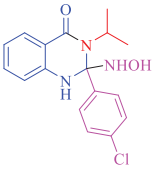
Table 2. Substrate scope for the synthesis of various 2-aryl-2-(hydroxyl amino)-3-alkyl or aryl 2,3-dihydroquinazolin-4(1*H*)-ones.

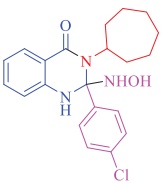


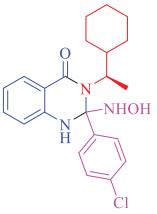

10a, 70%

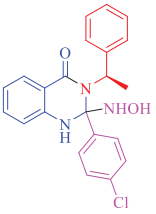

10b, 68%

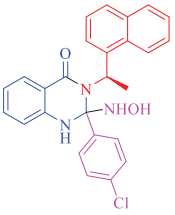

10c, 68%

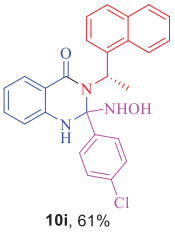

10d, 68%

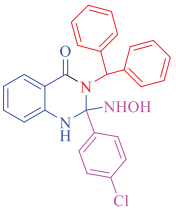

10e, 69%

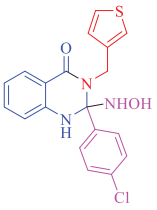

10f, 67%

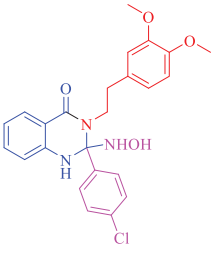

10g, 65%

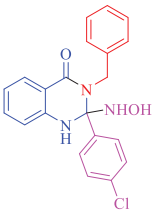

10h, 62%

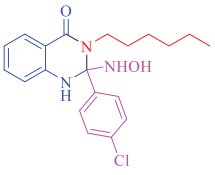

10i, 61%

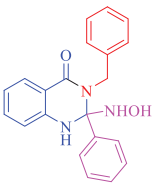

10j, 66%

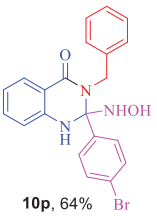

10k, 69%

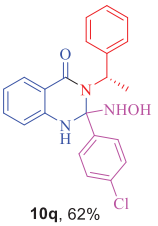

10l, 58%


10m, 68%


10n, 71%


10o, 62%

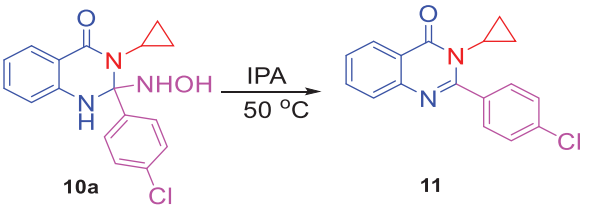

10p, 64%


10q, 62%

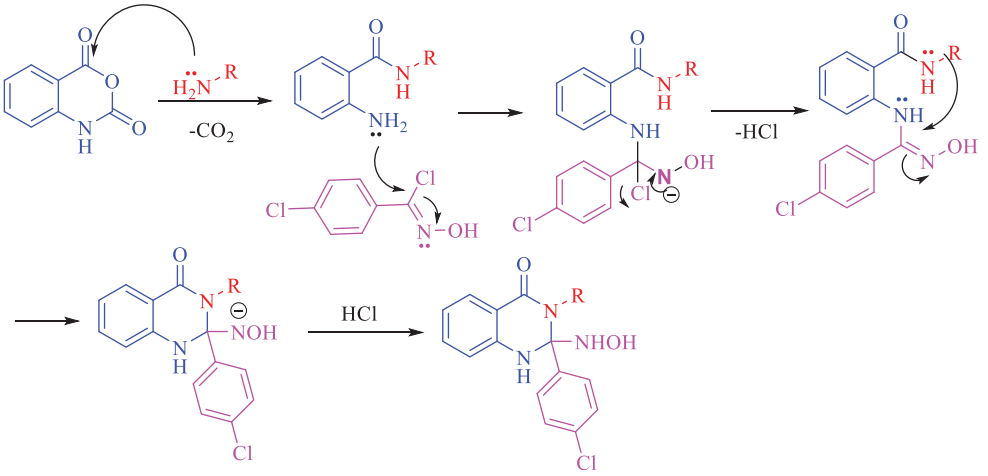
temperatures (Table 1). After screening the reaction in different stoichiometric ratios, the reaction was proceeded well in the presence of isopropylalcohol as a solvent and Et_3N as a base at 35 °C to get moderate yields.

Bold values represents final optimum conditions.

In continuation, after finding the optimum conditions in our hand, the substrate scope of the reaction has been studied with various amines and *N*-hydroxybenzimidoyl-chloride. To our delight, the reaction proceeded well with all types of amines like



Scheme 2. Synthesis of quinolines.



Scheme 3. The plausible reaction mechanism.

cyclopropyl, *n*-propyl, isobutyl, isopropyl, cycloheptyl, aryl, napthyl, benzyl, *n*-hexyl amines to get moderate yields (Table 2).

Nevertheless, to understand the feasibility of reaction on higher scale, we have demonstrated the reaction on a 10 g scale and gratifyingly we could amenable to reproduce the same results (Table 2, **10[a]**). Moreover, the synthetic application of these compounds were demonstrated by heating the compound (**10a**) in isopropylalcohol at 80–85 °C to get a biologically important quinolone by dehydroxylamination (Scheme 2). Furthermore, the possible reaction mechanism for this reaction has been proposed based on the reaction conditions and the experimental data (Scheme 3).

Experimental Section

General procedure for the synthesis of dihydroquinazolinone

To a stirred solution of isatoic anhydride (0.5 g, 3.1 mmol) in 1,4-Dioxane (15 mL), benzylamine (0.33 g, 3.1 mmol) was added at room temperature and the reaction temperature was slowly increased to 80–90 °C. The reaction mass was stirred for 3 h and water was added to the reaction mass at room temperature. The reaction mass was extracted with dichloromethane (2 × 20 mL) and separated both the layers. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to get 2-amino-benzamide.

To a solution of 2-amino-benzamide (250.0 mg, 1.41 mmoles, 1.0 eq.) in isopropylalcohol (10 mL), *N*-hydroxybenzimidoylchloride (540.0 mg 2.83 mmoles 2.0 eq.), triethylamine (360.0 mg 3.54 mmoles 2.5 eq.) were added and the reaction mass was stirred for 2 h. After completion of the reaction, the reaction mass was cooled to 0–5 °C, and the inorganic material was filtered. The solvent in the filtrate was evaporated under reduced pressure and the crude residue was purified by column chromatography (EtOAc/Pet-Ether (3:7) to get the pure product as a solid.

Analytical data for selected compounds

2-(4-Chlorophenyl)-3-cyclopropyl-2-(hydroxyamino)-2,3-dihydroquinazolin-4(1H)-one (10a)

Solid; Yield: 70%; ^{1}H NMR (400 MHz, DMSO-d_6):δ 10.92 (s, 1H), 10.00 (s, 1H), 8.60 (t, J = 5.6 Hz, 1H),7.52 (dd, J = 7.8 Hz, 1.4 Hz, 1H),7.44–7.35 (m, 4H),7.07–7.02 (m, 1H), 6.85–6.79 (m, 1H), 6.15 (d, J = 7.6 Hz, 1H), 2.91–2.87 (m, 1H), 0.74–0.70 (m, 2H), 0.62–0.58 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 170.0, 147.3, 140.4 134.0, 131.4, 131.0, 129.1(2 C), 129.0(3 C), 121.1, 119.4, 119.2, 23.0, 6.0(2 C); HRMS (ESI): *m/z* calcd for C17H16ClN3O2: 330.1004; found: 330.1003.

2-(4-Chlorophenyl)-2-(hydroxyamino)-3-propyl-2,3-dihydroquinazolin-4(1H)-one (10b)

Solid; Yield: 68%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 9.99 (s, 1H), 8.60 (t, J = 5.5 Hz, 1H), 7.55 (dd, J = 7.8, 1.4 Hz, 1H), 7.44–7.42 (m, 2H), 7.39–7.36 (m, 2H), 7.10–7.05 (m, 1H), 6.84 (t, J = 7.2 Hz, 1H), 6.17 (d, J = 7.9 Hz, 1H), 3.26–3.22 (m, 2H), 1.61–1.52 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 168.8, 147.8, 140.9, 134.2, 131.9, 131.0, 129.6(2 C), 129.1(2 C), 128.8, 122.0, 120.0, 119.7, 41.3, 22.8, 12.0; HRMS (ESI): *m/z* calcd. for $C_{17}H_{18}ClN_3O_2$: 332.1160; found: 332.1192.

2-(4-Chlorophenyl)-3-cycloheptyl-2-(hydroxyamino)-2,3-dihydroquinazolin-4(1H)-one (10e):

Solid; Yield: 69%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 9.91 (s, 1H), 8.40 (t, J = 7.8 Hz, 1H), 7.53 (dd, J = 7.7, 1.3 Hz, 1H), 7.44–7.41 (m, 2H), 7.39–7.35 (m, 2H), 7.09–7.04 (m, 1H), 6.83 (dd, J = 11.0, 4.1 Hz, 1H), 6.16 (d, J = 8.0 Hz, 1H), 4.01–3.93 (m, 1H), 1.92–1.84 (m, 2H), 1.68–1.40 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 147.8, 140.8, 134.3, 131.9, 130.9, 129.6(2 C), 129.1(2 C), 122.5, 120.1, 119.9, 119.7, 50.8, 34.7(2 C), 28.2(2 C), 24.5(2 C); HRMS (ESI): *m/z* calcd for $C_{21}H_{24}ClN_3O_2$: 386.1630; found: 386.1636.

2-(4-Chlorophenyl)-3-(3,4-dimethoxyphenethyl)-2-(hydroxyamino)-2,3-dihydroquinazolin-4(1H)-one (10 l):

Solid; Yield: 58%;^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 9.96 (s, 1H), 8.65 (t, J = 5.4 Hz, 1H), 7.51 (d, J = 6.7 Hz, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.07 (t, J = 7.3 Hz, 1H), 6.88–6.81 (m, 4H), 6.16 (d, J = 8.1 Hz, 1H), 4.37 (t, J = 7.0 Hz, 2H). 3.74 (s, 3H), 3.70 (s, 3H), 2.82 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0, 141.0, 140.8, 134.3, 133.9, 131.8, 131.2, 130.8, 129.6, 129.2, 129.1,

127.8, 126.7, 126.1, 126.0, 123.6, 123.0, 122.0, 120.0, 119.8, 45.2, 41.0(2 C), 22.0; HRMS (ESI): *m/z* calcd for $C_{24}H_{24}ClN_3O_2$: 454.1528; found: 454.1550.

Conclusions

In summary, we have developed a simple, metal-free reaction for the synthesis of novel functionalized dihydroquinazolinones. The reaction conditions are optimized and substrate scope of the reaction has been carried out to get moderate yields. Finally, the synthetic application of these compounds has also been demonstrated by synthesizing a quinolone pharmacore unit and similar kind of dihyroquinazolinone derivatives are under progress in our laboratory.

Acknowledgements

The authors would like to thank Dr. Reddy's Laboratory, Hyderabad for providing facilities to carry out this work. One of the authors Dr. Krishnaji acknowledges CHRIST (Deemed to be University) for funding Major Research Project (MRP # MRPDSC-1723).

ORCID

Krishnaji Tadiparthi http://orcid.org/0000-0003-1727-6305

References

[1] (a) Kunied, T.; Mutsanga, H. *The Chemistry of Heterocyclic Compounds; Palmer, B*, **2002**, 175. (b) Foye, W. O.; Thomas, L. *Foye's Principles of Medicinal Chemistry*, 6th ed.; Lippincott Williams & Wilkins: Philadelphia, 2007, p 36. (c) Czarnik, A. *Acc. Chem. Res.* 1996, *29*, 112–113. DOI: 10.1021/ar950256n.

[2] (a) Adriana, E. T.; Belmonte1, M. A.; Adam1, A.; Aquila1, B. M.; Boise, L. H.; Chiarparin, E.; Cidado1, J.; Embrey, K. J.; Gangl, E.; Gibbons, F. D.; et al. *Nature Comm.* **2018**, *9*, 5341. (b) *The Pharmaceutical Century: Ten Decades of Drug Discovery*; ACS Publications: Washington, DC, 2000.

[3] (a) Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1760–1763. DOI: 10.1002/1521-3773(20020517)41:10<1760::AID-ANIE1760>3.0.CO;2-3. (b) Tolman, C. A. *Chem. Rev.* 1977, *77*, 313–348. DOI: 10.1021/cr60307a002.

[4] (a) Jiang, J. B.; Hesson, D.; Dusak, B.; Dexter, D.; Kang, G.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721–1728. DOI: 10.1021/jm00168a029. (b) Cao, S. L.; Feng, Y. P.; Jiang, Y. Y.; Liu, S. Y.; Ding, G. Y.; Li, R. T. *Bioorg. Med. Chem. Lett.* 2005, *15*, 1915–1917. DOI: 10.1016/j.bmcl.2005.01.083.

[5] Chern, J. W.; Tao, P. L.; Wang, K. C.; Gutcait, A.; Liu, S. W.; Yen, M. H.; Chien, S. L.; Rong, J. K. *J. Med. Chem.* **1998**, *41*, 3128–3141. DOI: 10.1021/jm970159v.

[6] Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161–166. DOI: 10.1021/jm00163a027.

[7] (a) Pendergast, W.; Johnson, J. V.; Dickerson, S. H.; Dev, I. K.; Duch, D. S.; Ferone, R.; Hall, W. R.; Humphreys, J.; Kelly, J. M.; Wilson, D. C. *J. Med. Chem.* **1993**, *36*, 2279–2291. DOI: 10.1021/jm00068a004. (b) Kung, P. P.; Casper, M. D.; Cook, K. L.; Wilson-Lingardo, L.; Risen, L. M.; Vickers, T. A.; Ranken, R.; Blyn, L. B.; Wyatt, J. R.; Cook, P. D.; Ecker, D. J. *J. Med. Chem.* 1999, *42*, 4705–4713. DOI: 10.1021/jm9903500.

[8] (a) Rorsch, F.; Buscato, E.; Deckmann, K.; Schneider, G.; Zsilavecz, M. S.; Geisslinger, G.; Proschak, E.; Grosch, S. *J. Med. Chem.* **2012**, *55*, 3792–3803. DOI: 10.1021/jm201687d. (b) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S.; Lotti, V. J.; Chen, T. B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. S. *J. Med. Chem.* 1993, *36*, 3207–3210. DOI: 10.1021/jm00073a024.

[9] Mustazza, C.; Borioni, A.; Sestili, I.; Sbraccia, M.; Rodomonte, A.; Ferretti, R.; Giudice, M. R. D. *Chem. Pharm. Bull.* **2006**, *54*, 611–622. DOI: 10.1248/cpb.54.611.

[10] Malamas, M. S.; Millen, J. *J. Med. Chem.* **1991**, *34*, 1492–1503. DOI: 10.1021/jm00108a038.

[11] (a) Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; *Comprehensive Heterocyclic Chemistry III* Elsevier: Oxford, UK, **2008**. (b) Horton, D. A.; Bourne, G. T.; Smyth, M. L. *Chem. Rev.* **2003**, *103*, 893–930. DOI: 10.1021/cr020033s.

[12] (a) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787–9826. DOI: 10.1016/j.tet.2006.07.098. (b) Lee, S. H.; Son, J.-K.; Jeong, B. S.; Jeong, T.-C.; Chang, H. W.; Lee, E.-S.; Jahng, Y. *Molecules* **2008**, *13*, 272–300. DOI: 10.3390/molecules13020272.

[13] (a) Shaabani, A.; Maleki, A.; Mofakham, H. *Synth. Commun.* **2008**, *38*, 3751–3759. DOI: 10.1080/00397910802213802. (b) Vns Murthy, P.; Rambabu, D.; Rama Krishna, G.; Malla Reddy, C.; Prasad, K. R. S.; Basaveswara Rao, M. V.; Pal, M. *Tetrahedron Lett.* **2012**, *53*, 863–867. DOI: 10.1016/j.tetlet.2011.12.023. (c) Kiaee, S.; Masoumnia, A.; Maghsoodlou, M. *Res. Pharm. Sci.* **2012**, *7*, 5.(d) Darvatkar, N. B.; Bhilare, S. V.; Deorukhkar, A. R.; Raut, D. G.; Salunkhe, M. M. *Green Chem. Lett. Rev.* **2010**, *3*, 301–306. DOI: 10.1080/17518253.2010.485581. (e) Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814–3818. DOI: 10.1016/j.tetlet.2008.03.127. (f) Ghorbani-Choghamarani, A.; Taghipour, T. *Loc.* **2011**, *8*, 470–476. DOI: 10.2174/157017811796505025. (g) Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C. *Green Chem.* **2007**, *9*, 972. DOI: 10.1039/b700957g. (h) Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 908–910. DOI: 10.1002/anie.200804770. (i) Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475–3476. DOI: 10.1016/j.tetlet.2004.03.003. (j) Davoodnia, A.; Allameh, S.; Fakhari, A. R.; Tavakoli-Hoseini, N. *Chin. Chem. Lett.* **2010**, *21*, 550–553. DOI: 10.1016/j.cclet.2010.01.032. (k) Jianguang, Z.; Jie, F. *J. Org. Chem.* **2011**, *142*, 631. (l) Cheng, X.; Vellalath, S. K.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786–15787. DOI: 10.1021/ja8071034. (m) Bharate, S. B.; Mupparapu, N.; Manda, S.; Bharate, J. B.; Mudududdla, R.; Yadav, R. R.; Vishwakarma, R. A. *ARKIVOC* **2012**, *8*, 308. (n) Zeng, L.-Y.; Cai, C. *J. Heterocyclic Chem.* **2010**, *47*, 1035–1039. DOI: 10.1002/jhet.414.

[14] (a) Kumar, S. P.; Murthy, V. N.; Ganesh, K. R.; Rao, G. S.; Krishnaji, T.; Raghunadh, A. *Chem. Select* **2018**, *3*, 6836. (b) Jaganmohan, C.; Kumar, K. P. V.; Reddy, G. S.; Mohanty, S.; Kumar, J.; Rao, B. V.; Krishnaji, T.; Raghunadh, A. *Synth. Commun.* **2018**, *48*, 168–174. DOI: 10.1080/00397911.2017.1391291. (c) Murthy, V. N.; Nikumbh, S. P.; Tadiparthi, K.; Madhubabu, M. V.; Jammula, S. R.; Rao, L. V.; Raghunadh, A. *RSC Adv.* **2018**, *8*, 22331–22334. DOI: 10.1039/C8RA03308K. (d) Madhubabu, M. V.; Shankar, R.; More, S. S.; Basaveswara Rao, M. V.; Kumar, U. K. S.; Raghunadh, A. *RSC Adv.* **2016**, *6*, 36599–36601. DOI: 10.1039/C5RA28097D. (e) Raghavendra, R.; Ramamohan, K.; Raghunadh, M.; Suresh, A.; Praveen, B. M.; Kalita, K. S.; Laxminarayana, D.; Prasad, E.; Pal, B. *RSC Adv.* **2015**, *5*, 61575–61579. DOI: 10.1039/C5RA10928K. (f) R. Venkateshwarlu, V. N. Murthy, T. Krishnaji, S. P. Nikumbh, R. Jinkala, V. Siddaiah, M. V. M. babu, H. Rama Mohan and A. Raghunadh *RSC Adv*., **2020**, *10*, 9486–9491.