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THREE-STEP SYNTHESIS OF VARIOUS-1*H*-1,2,3-TRIAZOL-4-YL) METHYL) PYRIDO[2,3-B]PYRAZIN-2(1*H*)-ONES VIA C-N JUNCTION AND THEIR ANTI-PROLIFERATIVE ACTIVITY

Pavani .V and Jagadeesh Kumar Ega✉
Department of Chemistry, Chaitanya (Deemed to be University), Hanamkonda, Telangana-506001
✉Corresponding Author: jkjagadeeshkumare@gmail.com

ABSTRACT

Herein, we depict the reaction subbed with a blending bar originate the alkyne (III) and azide was added $CuSO_4$/sodium ascorbate of 1.2 eq K_2CO_3 and the response combination was mixed at RT for 16-18 h. After work up to bear the preferred 1-((1-aryl) - 1*H*-1,2,3-triazol-4-yl) methyl) quinoxalin-2(1*H*)- ones (IV a-IV j) item. This large number of mixtures were evaluated for their hostile to disease action against human malignant growth cell lines by means of MCF-7,A-549 and HeLa. *In vitro* against malignant growth movement uncovers that a couple of mixtures displayed strong inhibitory in an assortment of disease cell lines. Among them 1-((1-(2,4-dimethoxyphenyl)- 1H-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)- one (IV j) with 2,4-$OCH_3C_6H_3$ MCF-7 (3.64 ± 0.92), HeLa (4.62 ± 0.29), A-549 (8.02 ± 0.94) promising enemy of multiply movement .1-((1-(4-nitrophenyl)- 1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)- one(IVi) with p-$NO_2C_6H_4$ MCF-7 (4.15 ± 1.02), HeLa (6.43 ± 1.67), A-549 (10.74 ± 1.88) potent.1-((1-(2,4-dichlorophenyl)- 1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)- one (IV h) with 2,4-ClC_6H_3 MCF-7 (5.02 ± 1.38), HeLa (8.84 ± 2.01), A-549 (12.18 ± 2.82) great action. Etoposide utilized as a positive control.

Keywords: Pyrido-pyrazin, 1, 2, 3-Triazoles, Sharpless catalyst, Cycloaddition.

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INTRODUCTION

*T*riazole moieties are tempting associating entity[1], as fit for *H*- holding, which canister ideal in the restraining intent and solvency[2,3]. Mixtures containing a 1,2,3-Triazole portion show diverse exercises, for example, hostile to HIV[4] against microbial [5,6,7]. Pertaining to bring 1,2,3-triazole bunches keen on natural atoms, Cu(I)ion - accelerated cycloaddition response of azides and terminal alkynes[8,9] is a helpful methodology. In this context, we discuss the alteration by introducing 1,2,3-Triazole components keen on chromen-2-one.

It is accounted for that ultrasound light can accompany the evident response productivity with stretched rates and diminished response moment[10].Quinoxaline skeleton is an important part of a number of antibiotics that inhibit the growth of gram-positive bacteria and are found to be active against various transplantable tumors[11,12]. The quinoxaline derivatives flaunt a generous task in several biological activities like anti-cancer[13,14,15] and kinase-inhibition agents[16,17,18]. In this paper, a progression of 1*H*-1,2,3-triazol-4-yl) methyl) quinoxalin-2(1*H*)-ones were incorporated utilizing the copper sulfate/sodium ascorbate response.

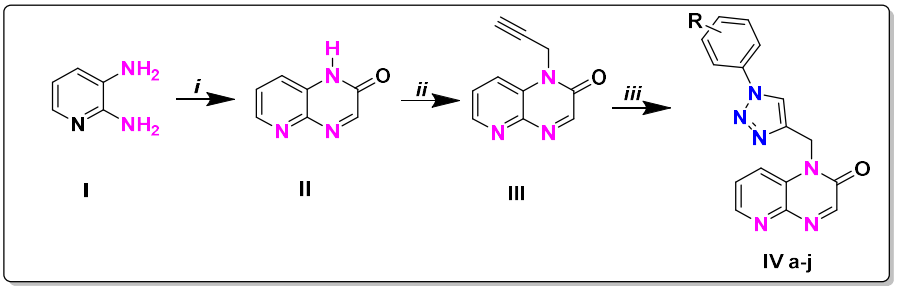

Fig.-1: Graphical Abstract

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EXPERIMENTAL

Synthesis of pyrido [2,3-b]pyrazin-2(1H)-one (II)

To an RB flagon containing 6 ml of MeOH, 10 mmol of half AcOH and 2,3-diamino pyridine (I) (10 mmol) were logically added under 5°C and the significant blend was enthused at a similar temperature for 3 h. The response combination with watered down with water and removed with EtOAc and water. The joined natural layers were evaporated over anhydrous metal sulfate and the overindulgence of ethyl acetic acid derivation was concentrated under vacuum to offer the unsophisticated items.

Synthesis of 1-(prop-2-yn-1-yl) pyrido[2,3-b]pyrazin-2(1*H*)-one (III)

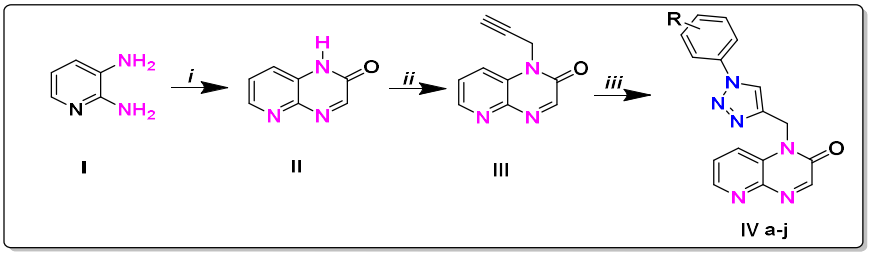
To anRB containing quinoxalin-2(1H)- one (II) (10 mmol) in dry DMF (10 mL), 28 mmol of Cs_2CO_3 were added segment shrewd up to 15 minutes and the 10 mmol of propargyl bromide was added and the subsequent combination was animated at room temperature for 4h. The response blend was removed two times with 10 ml of EAA and water individually. The natural layers were dried over anhydrous Na_2SO_4 and the overabundance of the natural layer was decreased under vacuum to give the unrefined item which was then additionally purged by segment chromatography by utilizing 3:7 EAA and hexane.

Synthetic Procedure for the of 1-((1-aryl)-1H-1,2,3-triazol-4-yl) methyl) quinoxalin-2(1*H*)-ones (IV a– IV j)

In a perfect, dry response vial outfitted with a blending bar were put the alkyne (III) (15 mmol) and aryl azide (20 mmol) was added copper sulfate/sodium ascorbate,DMSO/H_2O (9;1) and the response combination was stirred at 65^0C for 16-18 h. The joined natural layer was dried over anhydrous sodium sulfate, after filtration, the dissolvable vanished under vacuum, and the rough item acquired was cleansed by Colum chromatography (hexane/ ethyl acetate gradient in5:5) to afford the desired product and described in Scheme-1.

Reagents and Conditions

(i) Glyceraldehyde, MeOH, 5 ^{0}C, 3h.
(ii) Propargyl bromide, DMF, Cs_2CO_3, 4h, r.t.
(iii) Ar-N_3, $CuSO_4$/Sodium ascorbate, K_2CO_3, DMSO/H_2O, 65^0C, 16-18 h.



a: R = H, b:R = 2-$OCH_3C_6H_4$, c:R = $C_{10}H_7$, d:R = 2-FC_6H_4, e:R = 2-$CH_3C_6H_4$, f:R = 3-ClC_6H_4, g:R = 3-$OCH_3C_6H_4$, h:R = 2,4-ClC_6H_3, i:R = 4-$NO_2C_6H_4$, j:R = 2,4-$OCH_3C_6H_3$

Scheme-1: Synthesis of 1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1H)-one (IVa-IVj)

Material and Methods

Melting points were determined in open capillary and are uncorrected. Column chromatography was performed using silica gel purchased from Sigma-Aldrich and TLC was carried out using an aluminum sheet pre-coated with SiO_2 gel 60F254. PNMR data were recorded in DMSO on a Bruker Avance 400 MHz spectrometer. Joel SX spectrometer has been used the record the mass spectra. CHN analysis was carried out on a Carlo Erba EA analyzer. The combustion analyzer was found to be within the limits.

Spectral, Physical constant, yield and analytical data of compounds (IVa-IVj)

1-((1-phenyl-1*H*-1, 2, 3-triazol-4-yl) methyl) pyrido[2,3-b]pyrazin-2(1*H*)-one (IV a)

Light brown. 81%. m.p: 268–270°C; ^{1}HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.14 (s, 1H), 8.08 (s, 1H), 7.70 – 7.40 (m, 3H), 7.24 (t, 2H), 7.02 (dd, 1H), 6.63 (q, 1H), 5.07 (s, 1H), 4.77 (s,1H), 2.19 (s,

3H)MS:(ESI, m/z): 305, [M+H] ;Anal. Cacld for $C_{16}H_{12}N_6O$ C, 63.15; H, 3.97; N, 27.62. Found : C, 63.10; H, 3.91; N, 27.59%.

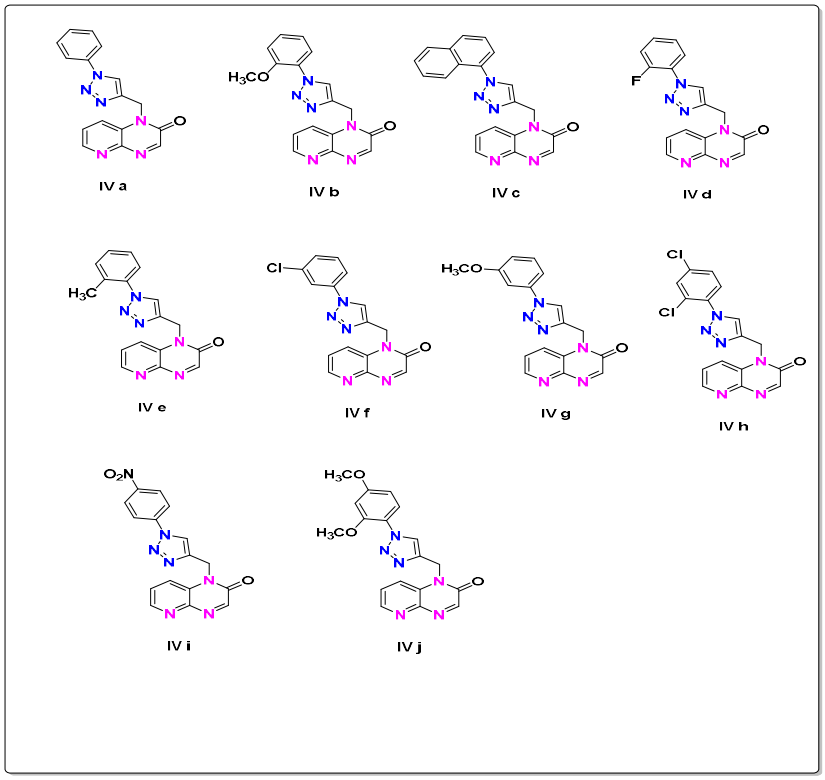


Fig.-2: Structures of entitled Compounds IVa–Ivj

1-((1-(2-methoxyphenyl)-1*H* -1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one (IV b)
Color: White.74%.m.p: 292–294°C; [1] HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.13 (s, 1H), 8.46 (d, 1H), 8.32 – 7.94 (m, 2H), 7.57 – 7.33 (m, 2H), 7.22 – 6.56 (m, 3H), 5.87 (s, 1H), 5.05 (s, 1H), 3.85 (s, 3H), MS:(ESI, m/z)335:[M+H]; Anal. Cacld for $C_{17}H_{14}N_6O_2C$, 61.07; H, 4.22; N, 25.14 . Found: C, 61.02; H, 4.12; N, 25.04%.

1-((1-(naphthalen-1-yl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one (IV c)
Color: Light brown. Yield. 80%. m.p: 276–278°C; [1] HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.16 (s, 1H), 8.41 – 8.15 (m, 1H), 8.14 – 7.89 (m, 2H), 7.78 (d, 1H), 7.69 – 7.33 (m, 5H), 6.66 (q, 1H), 4.95 (d, 2H), 2.19 (d, 3H) MS:(ESI, m/z): 355[M+H]; Anal. Cacld for $C_{17}H_{14}N_6O_2$ C, 67.79; H, 3.98; N, 23.72. Found: C, 67.73; H, 3.92; N, 23.62%.

1-((1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one (IV d)
Color: brown. Yield. 85%. m.p: 289–291°C; [1] HNMR (400 MHz, DMSO- d_6, δ ppm):δ 9.11 (s, 1H), 8.52 – 8.46 (m, 1H), 8.14 (d, 1H), 8.08 (s, 1H), 7.47 (t, 1H), 7.44 – 7.37 (m, 1H), 7.17 – 7.04 (m, 2H), 6.97 (t, 1H), 5.54 (s, 1H), 5.16 (s, 1H), MS:(ESI, m/z): 323 [M+H]; Anal. Cacld for $C_{16}H_{11}FN_6O$ C, 59.63; H, 3.44; N, 26.08. Found: C, 59.61; H, 3.40; N, 26.03%.

1-((1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one(IVe)
Color: Brownish white. Yield. 81%. m.p: 281–283°C; [1] HNMR (400 MHz, DMSO-d_6, δ ppm): δ 9.11 (s, 1H), 8.50 (s, 1H), 8.15 (s, 2H), 7.40 (d, 2H), 7.10 (d, 3H), 5.55 (s, 1H), 5.17 (s, 1H), 2.39 (s, 3H), MS:(ESI, m/z): 319 [M+H]; Anal. Cacld for $C_{17}H_{14}N_6O$ C, 64.14; H, 4.43; N, 26.40. Found: C, 64.10; H, 4.41; N, 26.38%

1-((1-(3-chlorophenyl)-1*H*-1, 2, 3-triazol-4-yl) methyl) pyrido[2, 3-b]pyrazin-2(1*H*)-one (IV f)
Color: white. Yield. 80%. m.p: 247–249°C; [1]HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.13 (s, 1H), 8.49 (d, 1H), 8.29 – 8.00 (m, 2H), 7.84 (d, 1H), 7.65 – 7.30 (m, 2H), 7.30 – 6.98 (m, 2H), 5.49 (s, 1H), 5.19 (s,

1H), MS:(ESI, m/z): 339 [M+H]; Anal. Cacld for $C_{16}H_{11}ClN_6O$ C, 56.73; H, 3.27; N, 24.81. Found: C, 56.70; H, 3.23; N, 24.79%.

1-((1-(3-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one (IV g)
Color: Pale white. Yield. 78%. m.p:268–270°C; [1] HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.14 (s, 1H), 8.48 (s, 1H), 8.11 (d, 2H), 7.62 – 6.98 (m, 5H), 5.56 (s, 1H), 5.16 (s, 1H), 3.80 (s, 3H), MS:(ESI, m/z): 335 [M+H]; Anal. Cacld for $C_{17}H_{14}N_6O_2$ C, 61.07; H, 4.22; N, 25.14. Found: C, 61.03; H, 4.20; N, 25.11%.

1-((1-(2,4-dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one (IV h)
Color: Red solid. Yield. 89%. m.p: 278–280°C; [1] HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.11 (s, 1H), 8.50 (s, 1H), 8.11 (d, 2H), 7.40 (ddd, 4H), 5.36 (d, *J* = 184.3 Hz, 2H), MS:(ESI, m/z): 375 [M+2]; Anal. Cacld for $C_{16}H_{10}C_{l2}N_6O$ C, 51.49; H, 2.70; N, 22.52. Found: C, 51.47; H, 2.68; N, 22.50%.

1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one(IV i)
Color: Yellow solid. Yield. 87%. m.p: 294–296°C; [1] HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.13 (s, 1H), 8.49 (d, 1H), 8.28 – 7.77 (m, 6H), 7.47 (t, 1H), 5.47 (s, 1H), 5.20 (s, 1H), MS :(ESI, m/z): 350 [M+H]; Anal. Cacld for $C_{16}H_{11}N_7O_3$ C, 55.02; H, 3.17; N, 28.07. Found: C, 55.00; H, 3.15; N, 28.05%.

1-((1-(2,4-dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-one (IV j)
Color: Yellow solid. Yield. 69%. m.p: 328–330°C; [1] HNMR (400 MHz, DMSO- d_6, δ ppm): δ 9.10 (s, 1H), 8.42 (s, 1H), 8.03 (d, 2H), 7.36 (d, 2H), 6.50 (d, 2H), 5.58 (s, 1H), 4.90 (s, 1H), 3.84 (s, 6H), MS:(ESI, m/z): 365 [M+H]; Anal. Cacld for $C_{18}H_{16}N_6O_3$ C, 59.34; H, 4.43; N, 23.07. Found: C, 59.31; H, 4.40; N, 23.05%.

RESULTS AND DISCUSSION

Anti-cancer Activity

MTT Protocol

The cytotoxic movement of the integrated mixtures was resolved to utilize the MTT test 1 × 104 cells/well were cultivated in 200 mL DMEM, enhanced with 10% FBS in each well of 96-well micro culture plates and hatched for 24 hours at 37ºC in a CO_2 hatchery. Following 48 hours in brooding 10 mL, MTT (5mg/mL) was added to each well and the plates were additionally hatched for four hours. Then, at that point, arrangement gems were broken up in 100 mL of DMSO, and absorbance at 570 nm frequency was recorded and the qualities are summed up in Table-1.

In-vitro Anticancer Activity

All the newly synthesized compounds (**IVa- IVj)** were additionally explored for in vitro enemy of disease profile over MCF-7 (bosom), A-549 (lungs) and HeLa (cervical) cell lines utilizing MTT examine utilizing etoposide as a positive control and got results were displayed in Table-1. Those analogs were exhibited IC50 esteems were shown promising movement, though; the remainder of the mixtures has shown moderate to low action when contrasted with standard etoposide. The design movement connections concentrate on uncovered that the compound (IVj) containing solid electron releasing 2,4-dimethoxy substituent on the phenyl ring joined to triazole skeleton was shown promising action with regards to electron-pulling out gatherings, the compound (IVi) with a p-NO_2 bunch on phenyl ring appended to triazole pharmacophore ring was displayed strong enemy of disease action. The compound (IVh) containing 2,4-dichloro bunch on the phenyl ring of triazole moiety showed improved action than the mixtures.

Table-1: *In-vitro* Cytotoxic Activity of Compounds (IV a– IV j) in (IC50 μM)

Entry	R	MCF-7 [b]	HeLa[c]	A-549 [d]
IV a	H	25.15 ± 8.31	43.56 ± 9.67	31.12 ± 9.31
IV b	2-$OCH_3C_6H_4$	31.42 ± 3.57	51.78 ± 4.89	12.16 ± 4.62
IV c	$C_{10}H_7$	31.52 ± 11.32	44.12 ± 10.65	29.41 ± 8.42
IV d	2-$FCH_3C_6H_4$	18.42 ± 6.54	21.78 ± 6.88	26.16 ± 7.62
IV e	2-$CH_3C_6H_4$	41.52 ± 12.32	34.12 ± 8.66	26.41 ± 7.48

IV f	3-ClC_6H_4	24.42 ± 4.48	21.94 ± 6.74	36.84 ± 6.24
IV g	3-$OCH_3C_6H_4$	18.41 ± 3.52	28.34 ± 5.48	19.23 ± 5.42
IV h	2,4-ClC_6H_3	5.02 ± 1.38	8.84 ± 2.01	12.18 ± 2.82
IV i	4-$NO_2C_6H_4$	4.15 ± 1.02	6.43 ± 1.67	10.74 ± 1.88
IV j	2,4-$OCH_3C_6H_3$	3.64 ± 0.92	4.62 ± 0.29	8.02 ± 0.94
Etoposide		3.08 ± 0.21	2.31±0.14	6.14±0.47

[a] Each data represents mean ±S.D values from three different experiments performed in triplicates. [b] MCF-7: human breast cancer cell line. [c] HeLa: human cervical cancer cell line. [d] A549: human lung cancer cell line.

CONCLUSION

The proficient technique depicted in this paper gives a wholly reliable strategy to the novel 1*H*-1,2,3-triazol-4-yl)methyl)pyrido[2,3-b]pyrazin-2(1*H*)-ones.

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REFERENCES

1. F.C. Odds, A.J.P. Brown, N.A.R. Gow, *Trends Microbiology*,**11**, 272(2003), http://doi.org/10.1016/s0966-842x(03)00117-3
2. D.K. Dalvie, A.S. Kalgutkar, J.P. Donnell, *Chemistry Research Toxicol*,**15**, 269(2002),http://doi.org/10.1007/978-0-387-77300-12
3. W.S. Horne, M.K. Yadav, M.R. Ghadiri, *Journal of American Chemical Society*, **126**,15366(2004), https://doi.org/10.1021/ja073513f
4. R. Alvarez, A. Karlsson, J. Balzarini, M.J. Camarasa, *Journal of Medicinal Chemistry*, **37**,4185 (1994), https://doi.org/10.1021/jm00050a015
5. M.J. Genin, D.A. Allwine, D.J. Anderson, B.H. Yagi, *Journal of Medicinal Chemistry*, **43**, 953(2000),http://doi.org/10.1021/jm990373e
6. D.R. Buckle, C.J.M. Rockell, H. Smith, B.A. Spicer, *Journal of Medicinal Chemistry*,**27**,223(1984), https://doi.org/ 10.1021/jm00368a021
7. L. M.J. Wywratt, A.E. Weber, *Bioorganic and Medicinal Chemistry Letters*, **10**,2111(2000), https://doi.org/10.1021/jm001051+
8. V.V. Rostovtsev, L.G. Green, K.B. Sharpless, *Angew. Chem*, **41**, 2596(2002),
9. C.W. Tornøe, C. Christiensen, M. Meldal, *Journal of Organic Chemistry*,**67**,3057(2002), http://doi.org/10.1021/jo011148j
10. J.T. Li,Y.J. Bian, H.J. Zang, T.S. Li, *Synthetic Communications*,**32**,547(2002), https://doi.org/10.2174/1570179054368509
11. Bailly, C., Echepare, S., Gago, F., and Waring, M., *Anti-Cancer Drug Design*,**14**,291(1999)
12. S.A. Raw, C.D. Wilfred, R.J.K. Taylor, *Chemical Communications*, **8**, 2286(2003), https://doi.org/10.1039/B307177B
13. C.W. Lindsley, Z. Zhao, W.H. Leister, R.G. Robinson, S.F. Barnett, D. Jones, G.D. Hartman, J.R.H. Huff, M.E. Duggan, *Bioorganic and Medicinal Chemistry Letters*, **15**,761(2005), https://doi.org/10.1016/j.bmcl.2004.11.011
14. M. Loriga, S. Piras, P. Sanna, *Farmaco*, **52**, 157(1997).
15. B. Srinivas, M. Ravinder, *Indian Journal of Chemistry*, **53**, 238(2014).
16. W. He, M.R. Meyers, B. Hanney, A. Spada, G. Blider, H. Galzeinski, D. Amin, K. Needle, *Bioorganic and Medicinal Chemistry Letters*, **13**, 3097(2003),https://doi.org/10.1016/S0960-894X(03)00655-3
17. J. Lee, W.V. Murray, R.A. Rivero, *Journal of Organic Chemistry*, **62**, 3874(1997), https://doi.org/10.1021/jo962412p
18. R.J. Holland, I.R. Hardcastle, M. Jarman, *Tetrahedron Letters*, **43**, 6435(2002), https://doi.org/10.1016/S0040-4039(02)01363-1

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