Research Article

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Synthesis of motexafin gadolinium: A promising radiosensitizer and imaging agent for cancer therapy

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Abstract: An improved, greener synthesis of motexafin gadolinium (MGd), a promising radiosensitizer and imaging agent that has the potential to treat or diagnose cancer, has been developed. Notably, this study addresses critical difficulties related to MGd synthesis and analysis of possible approaches, minimizing hazardous reagents/solvents, without column chromatography. The synthesis has been improved to enhance the overall yield and purity of MGd. The process changes outlined in this study are intended to lower production costs and time while maintaining the compound's characteristics. This synthesis of MGd is an important step toward attaining its full potential in the diagnosis and treatment of cancer.

Keywords: motexafin gadolinium, process development, radiosensitizer, imaging agent cancer therapy

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1 Introduction

Cancer remains a severe threat to human health around the world, demanding the development of novel treatment strategies that not only improve therapeutic efficacy but also reduce related side effects. The motexafin gadolinium (MGd) {4,5-diethyl-10,23-dimethyl-9,24-bis(3-hydroxypropyl)-16,-17-bis(3,hydroxypropyl)oxy-13,20,25,26,27-pentaazapentacyclo-[20.2.1.13,6.19,11.014,19]heptacosa-3,5,8,10,12,14,16,18,20,22,24-undecaene gadolinium} is a molecule in the texaphyrin class known as the Xcytrin as shown in Figure 1. MGd has emerged as a feasible candidate for improving the outcome of cancer radiotherapy. MGd is a small molecule that accumulates exclusively in tumor cells, making it a suitable radiosensitizer with the potential to boost the tumor-killing effects of radiation therapy while sparing healthy surrounding tissues. This one-of-a-kind property of MGd has drawn much interest in its ability to improve cancer treatment since it has the potential to improve cancer treatment efficacy [1].

These compounds have shown tremendous promise in terms of sensitizing tumor cells to ionizing radiation. The mechanism underlying radiosensitization involves the production of reactive oxygen species in the presence of oxygen, which can induce DNA damage and cell death when integrated with radiation therapy. Furthermore, the capacity of MGd to preferentially concentrate in tumor tissues by binding to biologically vital targets such as tumor vasculature and cell membranes contributes to its appeal as a radiosensitizer [2].

The MGd is a water-soluble gadolinium complex and clinical derivative, that exhibits notable selectivity for uptake and retention within tumors. This discernible selectivity is supported by extensive preclinical research and findings from early-stage clinical trials [3]. Extensively researched for its magnetic resonance imaging (MRI) detectability, MGd has been the subject of comprehensive studies involving both X-ray radiation therapy and, more recently, direct use as a

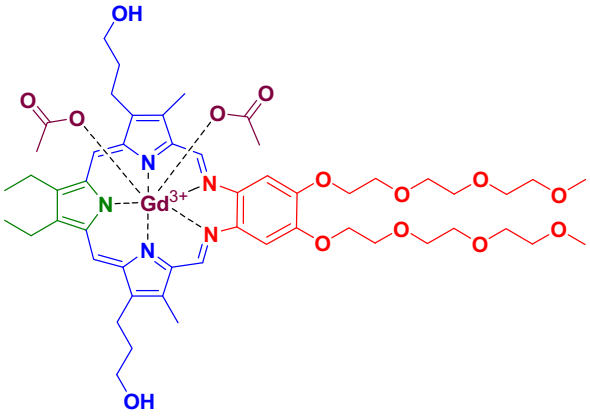


Figure 1: Chemical structure of MGd.

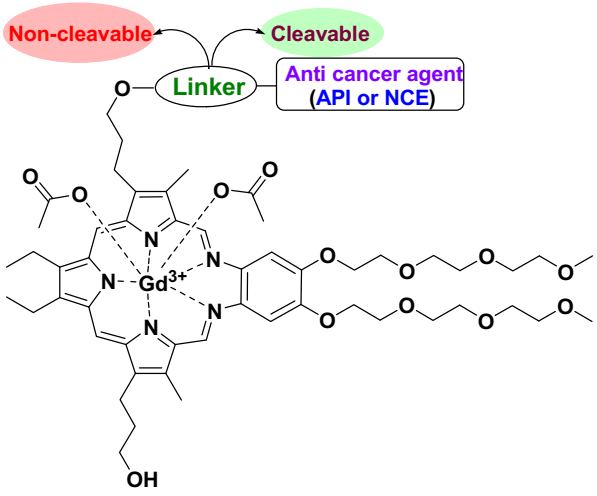


Figure 2: Hybridization approach using MGd for dual effect.

chemotherapeutic agent, either independently or in combination with other anticancer agents [4]. This strategy offers an additional benefit, as it enables the creation of conjugates featuring both cleavable and non-cleavable linkages. This versatility allows for a more comprehensive evaluation of the significance of drug release. Furthermore, these conjugates present an added advantage by potentially facilitating tumor-localized imaging and therapeutic activities specifically at targeted tumor sites [1].

MGd can selectively localize to cancerous lesions, as confirmed through various methods, including MRI. Recently, this core has been employed in the development of functionalized magnetic nanoparticles as dual-mode MRI contrast agents and concurrent hyperthermia agents [5]. Hence, MGd will be an ideal partner for novel hybrids to be effective multifunctional agents for cancer imaging and treatment, as shown in Figure 2.

To date, various studies have been conducted to investigate the potential of MGd, mostly in preclinical models and early-phase clinical trials. However, the literature only reports small-scale synthesis, which involves a complex and lengthy process with multiple steps, stringent reaction conditions, and column purifications. This results in lower overall yield due to intermediate purification steps and the use of hazardous chemicals that generate waste. Therefore, we attempted to alleviate safety concerns and mitigate isolation issues for lab scale-up by simplifying the synthesis process, reducing time and cost, and minimizing the need for intermediate purification by avoiding column purification. Our focus included using environmentally benign solvents and reagents, optimizing one-pot methods, exploring novel catalysts and reaction conditions, developing advanced purification methods to efficiently remove impurities, and utilizing techniques like crystallization and distillation. This article attempts to address this gap by focusing on the initial process development of MGd and contributes to the increasing knowledge of this promising radiosensitizer. Moreover, the successful development of MGd as a radiosensitizer is of paramount importance in the field of cancer therapy, as it can significantly improve the prognosis and quality of life of cancer patients.

2 Experimental section

2.1 Preparation of compound 8

To a stirred mixture of compound **3** (131.5 g, 1.16 mol, 1 eq) and compound **6** (220 g, 1.16 mol, 1 eq) that were dissolved in dry toluene (700 ml) under an N_2 atmosphere, DBU (300 ml, 2.32 mol, 2 eq) was added slowly and the solution was stirred for 16 h. The precipitation of white solid was observed. TLC shows completion of the reaction, R_f = 0.4 (10% EtOAc in Pet ether). The reaction mixture was neutralized by 1 N HCl until the pH of the solution became 7. The organic layer was separated and washed with water. To the toluene layer containing compound **7**, 10% aq NaOH (500 ml) was added and refluxed for 2 h. TLC shows completion of the reaction, R_f = 0.25 (50% EtOAc in Pet ether). The reaction mass was allowed to cool to room temperature and the organic layer was separated. To the aqueous layer, conc. HCl was added at 0°C to form a white solid. The obtained solid was collected by filtration followed by water wash. The obtained solid dried in a vacuum to furnish compound **8** (91 g, 47%) as a white solid (which turns brown color on standing for a long time). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.03 (t, 3H), 1.08 (t, 3H), 2.32 (q, 2H), 2.61 (q, 2H), 6.61 (d, 1H), 11.0 (1H, br), 11.9 (1H, br).

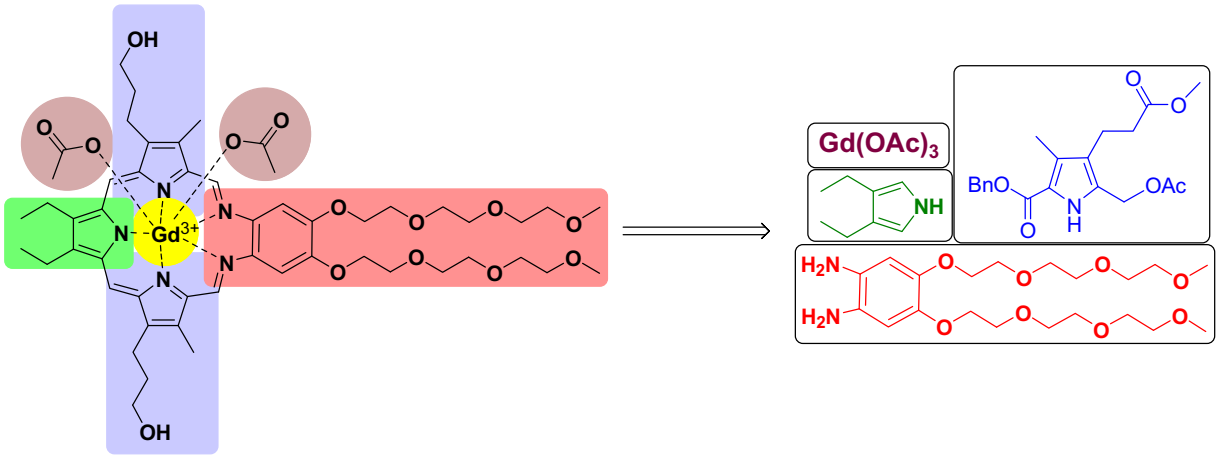


Figure 3: Retrosynthesis of MGd.

2.2 Preparation of compound 9

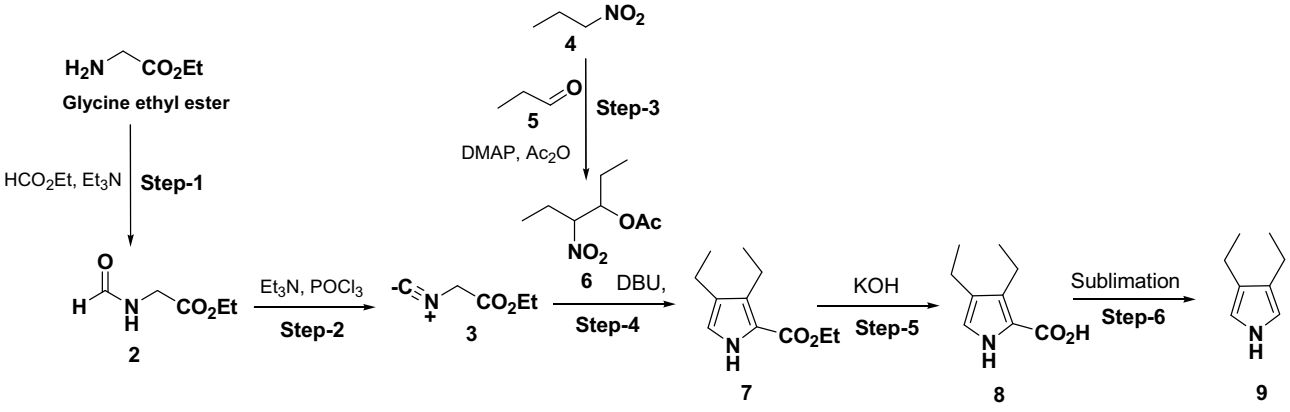
Compound **8** (90 g, 0.538 mol, 1 eq) was sublimed at 160°C for 2 h. TLC shows completion of the reaction, R_f = 0.8 (50% EtOAc in Pet ether). Compound **9** (53 g, 80%) was isolated by fractional distillation as a light brown liquid (moderately unstable, stored in the freezer, solidified at −20°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, 6H), 2.49 (q, 4H), 6.58 (d, 2H), 7.92 (s, 1H).

2.3 Preparation of compound 16

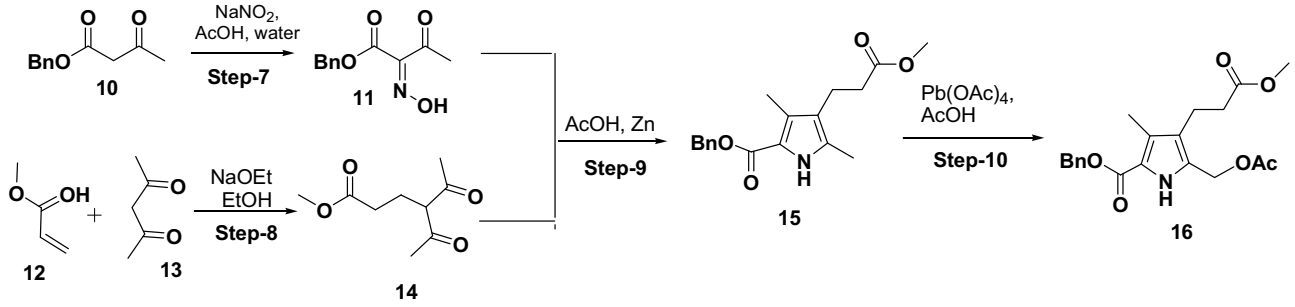
To a suspension of compound **15** (400 g, 1.26 mol, 1 eq) in glacial acetic acid (5 l), lead tetra acetate (562.4 g, 1.26 mol, 1 eq) was added portion wise and stirred for 5 h at 25–30°C. TLC shows completion of the reaction, R_f = 0.25 (30% EtOAc in Pet ether). The reaction mixture was quenched in ice-cold water to get precipitation, filtered, and washed with water. Crude was recrystallized from aqueous acetone and dried under high vacuum to get compound **16** (336 g, 71%) as white powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (s, 3H), 2.29 (s, 3H), 2.46 (t, 2H), 2.77 (t, 2H), 4.12 (s, 3H), 5.05 (s, 2H), 5.31 (s, 2H), 7.34–7.42 (m, 5H), 9.00 (br s, 1H).

2.4 Preparation of compound 18

To a solution of compound **17** (30 g, 182.88 mmol, 1 eq) in CH_2Cl_2 (300 ml), TEA (46.20 g, 457.20 mmol, 2.5 eq), Tosyl chloride (53.50 g, 274.32 mmol, 1.5 eq), and a catalytic amount of DMAP (300 mg) were added at 0°C. The reaction mixture was stirred for 3 h at 27°C. TLC shows completion of the reaction, R_f = 0.6 (25% EtOAc in Pet ether). The reaction mixture was washed with water (300 ml) followed by brine (300 ml), dried over anhydrous Na_2SO_4, and concentrated to obtain 40 g crude compound **18** oily liquid, used as it is without further purification.



Scheme 1: Telescopic synthesis of compound **9**.



Scheme 2: Synthesis of compound **16**.

2.5 Preparation of compound 19

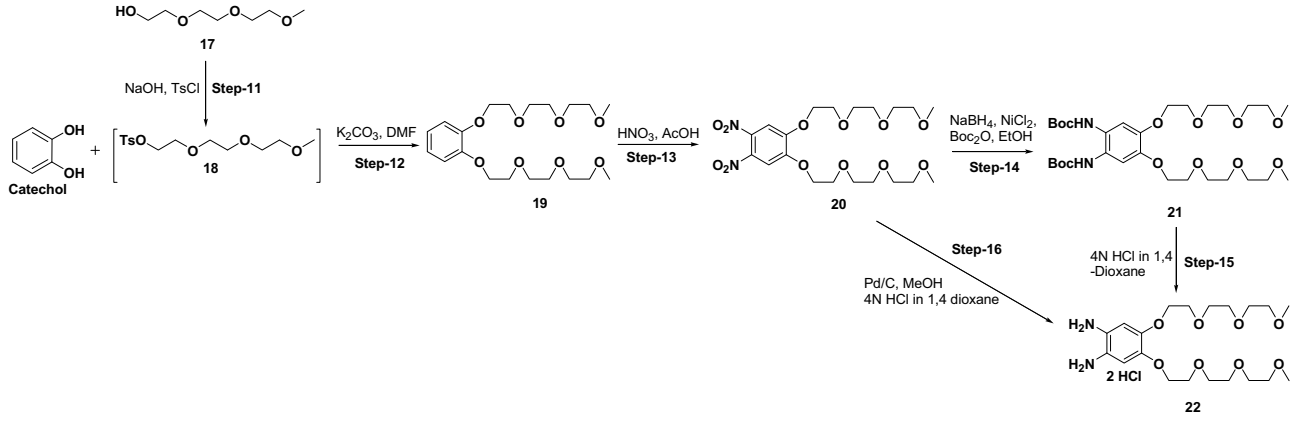
To the solution of catechol (5.5 g, 49.99 mmol, 1 eq) in DMF (50 ml), K_2CO_3 (27.61 g, 199.98 mmol, 4 eq) followed by a solution of compound **18** (39.79 g, 124.97 mmol, 2.5 eq) in DMF (30 ml) was added at RT under N_2. The reaction mixture was allowed to 80°C for 3 days. TLC shows completion of the reaction. The mixture was allowed to cool down to ambient temperature before pouring into deionized water (500 ml). Methyl *tert*-butyl ether (2 × 300 ml) was used to extract the product and the combined organic phases were dried over $MgSO_4$ and removed *in vacuo*. A yellow oil was obtained and dried under a reduced vacuum to obtain **19** (38.5 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.92 (m, 4H, ArH), 4.16 (t, J = 6.6 Hz, 4H, O–CH_2), 3.85 (t, J = 6.9 Hz, 4H), 3.4–3.7 (m, 16H), 3.37 (s, 6H); MS-EI m/z 403.2 $(M+H)^+$.

2.6 Preparation of compound 20

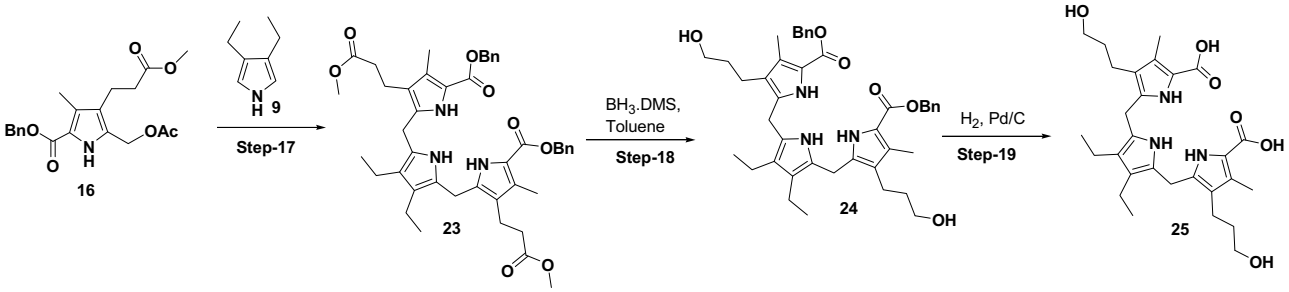
Compound **19** (35 g, 87.08 mmol, 1 eq) was dissolved in AcOH (35 ml) and cooled to 0°C by using ice–salt mixture. Fuming HNO_3 (35 ml) [Caution! nitric acid is highly corrosive liquid and overcharging may generate exotherm and release significant of toxic NO_x gas, must be handled carefully with all necessary safety precaution and PPE in a certified chemical fume hood] was added drop wise by maintaining temperature between 0 and 5°C and stirred for 3 h at same temperature. TLC shows completion of the reaction, R_f = 0.6 (5% MeOH in $CHCl_3$). The reaction mixture was quenched with ice water. Extracted with DCM (3 × 100 ml), the combined organic layer was washed with 5% aq KOH solution repeatedly followed by brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated. The obtained crude was dissolved in a mixture of acetone and *n*-hexane under constant stirring at −5°C. The resulting precipitate was collected by filtration to obtain compound **20** (35 g, 82%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.36 (s, 6H), 3.52–3.75 (m, 16H), 3.90 (t, 4H), 4.33 (t, 4H), 7.48 (s, 2H); MS-EI m/z 493.2 $(M+H)^+$.

2.7 Preparation of compound 21

To a solution of compound **20** (10 g, 20.32 mmol, 1 eq) in absolute EtOH (200 ml), $NiCl_2{\cdot}6H_2O$ (0.97 g, 4.06 mmol, 0.2



Scheme 3: Synthesis of compound **22**.



Scheme 4: Synthesis of compound **25**.

eq) and $(Boc)_2O$ (35.43 g, 162.56 mmol, 8 eq) were added. The reaction mixture was cooled to 0°C, $NaBH_4$ (4.8 g, 142.27 mmol, 7 eq) was added slowly portion wise and stirred for 30 min. To this, TEA (8.5 ml, 60.96 mmol, 3 eq) was added and stirred for 1 h. TLC shows completion of the reaction, R_f = 0.6 (5% MeOH in $CHCl_3$). The reaction mixture was concentrated and the crude was purified by using silica gel column chromatography (230–400 mesh, 5–10% MeOH in DCM as mobile phase). Product fractions were collected and concentrated to obtain the desired compound **21** (6.3 g, 49%) as light-yellow gummy liquid. ^{1}H NMR (DMSO d_6, 400 MHz): δ 1.48 (s, 18H), 3.21 (s, 6H), 3.29 (t, 4H), 3.42 (t, 4H), 3.50–3.59 (t, 8H), 3.73 (t, 4H), 4.00 (t, 4H), 7.02 (s, 2H), 8.26 (s, 2H); MS-EI *m*/*z* 631.4 $(M-H)^+$.

2.8 Preparation of compound 22 (method A)

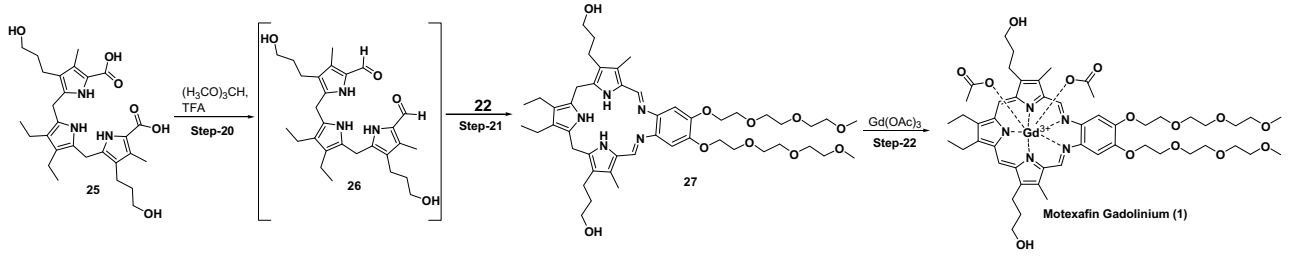
To a solution of compound **21** (6.3 g, 9.968 mmol, 1 eq) in anhydrous 1,4-dioxane (60 ml), 4 M HCl in 1,4-dioxane (50 ml) was added slowly at 0°C and stirred for 4 h at 27°C. TLC shows completion of the reaction, R_f = 0.05 (10% MeOH in $CHCl_3$). The reaction mixture was concentrated. The crude compound was triturated with ether (3 × 50 ml), decanted, and dried under a high vacuum to obtain compound **22** (4.4 g, 87%) as a brown gummy solid.

2.9 Preparation of compound 22 (method B)

To a solution of compound **20** (24 g, 48.73 mmol, 1 eq) in methanol (240 ml), 10% palladium on carbon was added carefully (2.4 g, ~50% wet) (Caution! pyrophoric! should be used patiently with PPE and safety precautions) and stirred in an autoclave under hydrogen pressure. TLC shows completion of the reaction, R_f = 0.05 (10% MeOH in $CHCl_3$). The catalyst was filtered carefully (Caution! expected to cause a fire while filtration of Pd/C in methanol in open air) and washed twice swith methanol. The filtrate was evaporated to half and cooled to 0°C. 4 M HCl in 1,4-dioxane (75 ml) was added slowly at 0–5°C and stirred for 1 h at room temperature. Reaction mass concentrated under reduced pressure and triturated with methyl *tert*-butyl ether, dried under high vacuum to afford compound **22** (19.7 g, 80%) as a brown gummy solid. ^{1}H NMR (DMSO d_6, 400 MHz): δ 3.32 (s, 6H), 3.35–3.60 (m, 16H), 3.72 (t, 4H), 3.98 (t, 4H), 5.60–6.45 (s, br, 4H), 6.72 (s, 2H); MS-EI *m*/*z* 433.3 $(M+H)^+$.

2.10 Preparation of compound 23

To a stirred mixture of compound **16** (300 g, 775.5 mmol, 1 eq) and compound **9** (48 g, 387.7 mmol, 0.5 eq) in methanol



Scheme 5: Synthesis of the MGd.

(3 l), a catalytic amount of PTSA (13.5 g, 77.5 mmol, 0.1 eq) was added at 28°C under N_2 atmosphere. The reaction mixture was heated to 60°C and maintained for 2 h. TLC shows completion of the reaction, R_f = 0.7 (50% EtOAc in pet ether). The reaction mixture was cooled to 0°C, stirred for 30 min, and filtered. The solid was washed with cold methanol (500 ml). The solid was dried under a high vacuum to get compound **23 (**180 g, 30%) as white powder. mp 161–162°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 (t, 6H), 1.89 (s, 6H), 2.30–2.50 (m, 9H), 2.64 (t, 4H), 4.06 (t, 4H), 3.78 (t, 4H), 3.55 (s, 1H), 5.00 (s, 4H), 7.20 (s, 1H), 7.22–7.35 (m, 10H), 8.25 (s, 1H), 10.88 (s, 1H).

2.11 Preparation of compound 24

To cold solution of compound **23** (175 g, 224.87 mmol, 1 eq) in toluene (1.75 l), dimethyl sulfide complex (64.08 ml, 674.61 mmol, 3 eq) [Caution! wear the appropriate PPE and safety measures] was added drop wise at 0°C–5°C, heated to 50°C and stirred for 5 h. TLC shows completion of the reaction, R_f = 0.2 (5% MeOH in CH_2Cl_2). The reaction mixture was cooled to 0°C, quenched with water (1.0 l), and stirred for 1.0 h. To the organic layer, 5% aq sodium hydroxide solution (1.0 l) was added and stirred for 1 h, separated, and washed with 1.0 N HCl (300 ml) followed by 10% aq sodium chloride solution (300 ml), dried over anhydrous Na_2SO_4, and concentrated. The crude compound was suspended in cold methanol (1 l) and stirred for 10 min. Filtered, washed with ice cold methanol (100 ml) and recrystallized from DCM/ethanol. The solid was collected and dried under a high vacuum to obtain compound **24** (70 g, 43%) as off-white solid (which turns to pink on long standing). mp 172–173°C; ^{1}H NMR (DMSO d_6, 400 MHz): δ 0.95 (t, 6H), 1.39 (t, 4H), 2.13 (s, 6H), 2.30–2.40 (m, 9H), 3.37 (s, 4H), 3.67 (s, 4H), 4.36 (t, 2H), 5.23 (s, 4H), 7.28–7.49 (m, 11H), 9.42 (s, 1H).

2.12 Preparation of compound 25

To a solution of compound **24** (67.5 g, 97.35 mmol, 1 eq) in dry THF (675 ml), wet 10% Pd/C (21 g, 30% w/w) was added in an autoclave under hydrogen pressure (3 kg·cm^{-3}) and stirred for 5 h. TLC shows completion of the reaction, R_f = 0.15 (10% MeOH in CH_2Cl_2). The reaction mixture was filtered through a celite bed and washed with THF (300 ml). The combined filtrate was concentrated and suspended in DCM (300 ml). Stirred for 10 min, filtered and washed with ice cold DCM (150 ml). The solid was collected and dried under a high vacuum to obtain compound **25** (37.5 g, 75%) as white solid (which turns to pink on long standing). ^{1}H NMR (DMSO d_6, 400 MHz): δ 0.98 (t, 6H), 1.08 (t, 1H), 1.38 (t, 4H), 2.13 (t, 6H), 2.20–2.32 (m, 8H), 3.57 (m, 2H), 3.69 (s, 4H), 4.36 (s, 2H), 9.50 (s, 1H), 10.69 (s, 2H), 11.78 (s, 2H).

2.13 Preparation of compound 26

To a suspension of compound **25** (35 g, 66.40 mmol, 1 eq) in trimethyl orthoformate (210 ml), trifluoroacetic acid (210 ml) was added drop wise at −20°C and stirred for 1 h at 27°C. TLC shows completion of the reaction, R_f = 0.25 (10% MeOH in CH_2Cl_2). The reaction mixture was poured into crushed ice and extracted with DCM (3 × 200 ml). The combined organic layer was washed with brine (200 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain compound **26** (17.5 g, 53%) as dark brown solid. The crude compound was used in the next step without any purification.

2.14 Preparation of compound 27

To stirred mixture of compound **26** (17.5 g, 36.37 mmol, 1 eq) and compound **22** (18.32 g, 40 mmol, 1.1 eq) in dry methanol (300 ml), 4 M dry HCl in 1,4-dioxane (25 ml) slowly at 27°C was added under an argon atmosphere. The reaction mixture was heated to 50°C and maintained for 4 h. TLC shows completion of the reaction, R_f = 0.25 (10% MeOH in CH_2Cl_2). The reaction was cooled to 27°C, and 50 g of activated charcoal was added and stirred for 30 min. The dark suspension was filtered through celite to remove the carbon and the filtrate was concentrated. The crude was dried under a high vacuum to obtain 32.5 g of compound **27** as a dark red solid. The crude compound was crystallized from iso-propanal and heptane to obtain compound **27** (20 g, 63%) as a scarlet red solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.10 (t, 6H), 1.76 (p, 4H), 2.36 (s, 6H), 2.46 (q, 4H), 2.64 (t, 4H), 3.29 s, 6H), 3.31 (t, 4H), 3.43–3.85 (m, 20H), 4.10 (s, 4H), 4.22 (t, 4H), 7.45 (s, 2H), 8.36 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 9.18, 9.41, 16.79, 17.08, 18.41, 20.83, 21.00, 30.73, 34.09, 59.04, 62.18, 70.66, 70.83, 71.34, 71.43, 71.80, 71.86, 72.96, 103.69, 122.34, 123.22, 125.45, 125.65, 130.92, 141.75, 150.26; UV/vis: nm 481, 370; MS-EI *m*/*z* 878.5 $(M+H)^{+;}$ HPLC purity: ~87.58%.

2.15 Preparation of compound 1

The $Gd(OAc)_3$ (18 g, 53.36 mmol, 1.5 eq) was dissolved in dry MeOH (250 ml) and TEA (56 ml, 391.2 mmol, 11 eq) was

added at 27°C. The reaction mixture was bubbled with air for 10 min, and a solution of compound **27** (31.2 g, 35.56 mmol, 1 eq) in dry MeOH (250 ml) drop wise was added. The reaction mixture was heated to reflux and maintained for 3 h with continuous air bubbling through the balloon. TLC shows completion of the reaction, R_f: 0.3 (15% MeOH in DCM). The reaction mixture was cooled to room temperature, filtered through celite and thoroughly washed with MeOH (150 ml). The filtrate was concentrated in a vacuum. The crude was suspended in acetone (300 ml), stirred for 15 min, and filtered. The solid was washed with 100 ml of cold acetone. The solid was dissolved in 500 ml of 1:9 mixture of water in MeOH and stirred with acetic acid-washed zeolite (2 × 100 g). Filtered and concentrated. The crude compound was dissolved in Millipore water (300 ml) and passed through acetic acid-washed Ambersep resin (Ambersep 900 OH, flow rate 5 ml·min^{-1}). Collected fractions were concentrated in a vacuum and the solid obtained was triturated with acetone (3 × 100 ml), filtered, and dried under a high vacuum for several hours to obtain compound **1** (13.2 g, 27%) as a dark green microcrystalline solid. UV/vis: nm 318, 342, 418, 478, 739; MS-EI *m*/*z* 1089.5 [M-(mPEG3-OH-Ac)]$^+$; HPLC purity: ~95.86%.

3 Results and discussion

This study addresses one of the most important aspects of the use of MGd, such as its use in efficient synthetic approaches for gram scale preparation. The goal is to understand each chemical step to develop a better process, subsequently translate for large-scale production, and pave the way for successful clinical translation. However, multiple critical issues persist in the reported protocols, including multistep process, column chromatography, hazardous reagents, low overall yields, extended reaction times, and significant preparation costs. We focused primarily on improving the process for the preparation of penultimate intermediates of MGd, as shown in Figure 3.

Ethyl isocyanoacetate (**3**) was synthesized from the commercially available glycine ethyl ester [6]. Synthesis of compound **7** (3,4-diethylpyrrole-2-carboxylate) was achieved by one-pot synthesis as reported in the literature [7]. The economical and commercially available DMAP [6] was used to achieve the Henry reaction (using 1-nitropropane and propionaldehyde) and acetylation (with acetic anhydride) simultaneously instead of DBU and sulfuric acid to get compound **6**. The Magnus–Schöllkopf–Barton–Zard cyclization was achieved in dry toluene using compound **3** and compound **7** instead of dry THF. The toluene layer was directly subjected to hydrolysis with NaOH to avoid extraction, separation, and distillation of organic solvents such as ethyl acetate or diethyl ether [8]. By following an acid–base purification technique, excellent purity of compound **8** was achieved. Compound **8** was sublimed at 160°C for 2 h and subsequently isolated by fractional distillation [6,9]. Hence, compound **9** was successfully optimized without column chromatography purification as shown in Scheme 1.

Benzyl acetoacetate (**10**) was treated with a solution of sodium nitrite to get oxime **11**. The methyl 4-acetyl-5-oxohexanoate (**14**) was prepared via a sodium ethoxide-catalyzed Michael addition reaction of acetylacetone (**13**) to methyl acrylate (**12**). The synthesis of pyrrole **15** was achieved by a one-pot zinc metal-catalyzed reduction of oxime **11** to corresponding amine followed by *in situ* condensation with **14**. Compound **15** was treated with lead tetraacetate in acetic acid [10] without acetic anhydride [2] to furnish acetoxyl derivative **16** as shown in Scheme 2.

The synthesis of 1-bromo-2-(2-(2-methoxyethoxy)ethoxy) ethane [11] from alcohol **17** by the Appel reaction was avoided due to the hazardous bromine and column purification to purge by-product (TPPO) [12]. The (2-[2-(2-methoxyethoxy) ethoxy]ethanol **17** was transformed to tosyl derivative **18** by treatment with tosyl chloride followed by a nucleophilic substitution reaction with the phenoxide ion of catechol to afford compound **19**. Dinitro derivative **20** was obtained by nitration with nitric acid in acetic acid followed by recrystallization by isopropyl alcohol [13]. Considering its toxicity, safety, and environmental risk, hydrazine hydrate was avoided as a hydrogen source under reflux [14] for the reduction of nitro to amine [15]. Initially, compound **20** was converted to Boc-protected amine **21** by one-pot reduction of nitro to amine by sodium borohydride (7 eq) and a catalytic amount of nickel chloride (0.1 eq) followed by Boc protection using Boc anhydride. Subsequently, Boc deprotection was achieved by 4 N HCl in 1,4 dioxane, which was isolated as HCl salt of diamine **22** to avoid further oxidation/decomposition of the diamine. In the additional protection/deprotection step, an excess catalyst was used, and the column was easily removed by switching the catalyst to Pd/C under a hydrogen atmosphere [16] as shown in Scheme 3.

Scheme 4 shows that *p*-toluene sulfonic acid catalyzed the addition of electron-rich pyrrole (**9**) to compound **16** at the C2 and C5 positions of **9**, effectively displacing acetate moiety **16** to afford compound **23**. Considering the tedious and time-consuming workup and hazards associated with extremely reactive lithium aluminum hydride [17], commonly used reducing agents for converting esters to alcohols were avoided. Despite being more reactive than BH_3·DMS, BH_3·THF is available commercially as a 1 M THF solution only. However, the more stable BH_3·DMS is a less expensive and readily available neat reagent [18]. Moreover, economical and easily

recyclable/reusable toluene is used as a solvent with BH_3. DMS was used instead of THF [19] to obtain the alcohol derivative **24**. Debenzylation was achieved by traditional hydrogenolysis of carboxylic esters using 10% Pd/C to afford diacid derivative **25.**

Compound **25** was transformed to the corresponding aldehyde derivative **26** via a decarboxylation–formylation sequence similar to a Clezy formylation by treatment with trimethyl orthoformate in trifluoroacetic acid [2]. Acid-catalyzed imine condensation of dialdehyde **26** with the aromatic diamine **21** resulted in a macrocyclic core of Texaphyrin **27**, which was subsequently treated with $Gd(OAc)_3$ to obtain the desired final product, as shown in Scheme 5.

The process development of MGd represents a critical advancement in the quest to harness its potential as a promising radiosensitizer for cancer therapy. This research endeavor has addressed several key aspects related to the synthesis and optimization of MGd, shedding light on the path toward its successful lab scale-up. The improved synthesis method described herein offers increased efficiency and enhanced yield, mitigating some of the challenges associated with the gram-scale synthesis of MGd. These modifications not only make MGd more accessible for research purposes but also have the potential to reduce synthesis time and cost. This process reduces overall waste generation and obeys the majority of green chemistry principles, as hazardous substances are replaced with less hazardous alternatives, and greener solvents, avoiding the excessive use of solvents [20,21].

In conclusion, the process development of MGd represents a vital step in revealing the full potential of this compound for further fight against cancer. The synthesis described in this report overcomes numerous challenges commonly encountered in current preparative methods. This approach not only demonstrates the feasibility of producing MGd efficiently and safely but also underscores its significance as a promising adjunct to radiation therapy.

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